# History of HORIBA Medical Products to Contribute to the In Vitro Diagnostic Testing

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Medical and health care is one of the greatest topic on development on society development and sustaining. Most of the medical and health care treatment is based on diagnosis based on the result from various testing, analysis and interviews. In vitro diagnostic medical devices are critical testing source to achieve necessary care to the patient. This article describes how HORIBA medical have been supporting the medical field by providing IVD medical device.

## Introduction

Globally, over several trillion dollars of annual spending is recorded for medical practices, with an increasing trend every year. Of the practices, while it is needless to say that diagnoses and treatments of diseases are essential parts, testing also plays a crucial role in supporting diagnoses, treatments and management of outcomes thereof.

In particular, data obtained on in vitro diagnostic (IVD) medical devices, which enable quantitative and qualitative reporting of intracorporeal signals that are invisible to our eyes, are considered highly important indicators in clinical practice.

Here, I describe IVD devices' roles and HORIBA Medical's engagement in hematology and clinical chemistry, basic but important fields in clinical testing, and also in the point of care testing (POCT) field, which places emphasis on speed and simple procedures in the recent ever-diversifying medical practices.

## Hematology field

### What is Hematology?

Blood circulating in the human body transports substances essential to maintain life and eliminates waste products. Depending on the physical state, substances found in blood for transportation or removal vary, making blood the most fundamental sample in understanding the body's condition.

Blood consists of a fluid component called plasma and blood cells, which travel through the plasma. Hematology in the context of clinical testing mainly refers to blood cell analysis, i.e., cell counting (white blood cells [WBCs], red blood cells [RBCs], and platelets) and RBC hemoglobin concentration, among others. Analysis of coagulation or hemostasis is related to hematology testing since these phenomena are activated by coagulation- or fibrinolysis-associated platelet reactions, but here hematology limited to blood cell counting is discussed.

### Hematology testing (significance)

Blood cell counting, i.e., complete blood cell count (CBC), refers primarily to RBC, WBC, and platelet counting.

Briefly, an increase or decrease in these blood cells reflects a certain state of the body: Anemia condition is reflected in the count of RBCs, transporters of oxygens throughout the body; the state of protection against foreign materials that have entered the body (i.e., immunity) in the count of WBCs, which have an immunological function; and the tendency to develop blood clots in the count of platelets, which can induce blood coagulation.

In combination with other test results, the disease state or condition is diagnosed. The CBC is the simplest test and is highly useful for screening that leads to a definitive diagnosis.

In principle, the most primitive method of blood cell counting is estimation by manual microscopic counting.

As a simple method using relatively readily available tools (a general microscope and a hemocytometer), microscopic counting is still employed nowadays in some situations; however, since around the 1950s, automated counting with higher efficiency has been increasingly in demand as the testing frequency has risen and the issue of measurement errors associated with laboratory staff skills has surfaced.

The advent of a blood cell counter based on the electrical resistance method, taking advantage of blood cells' dielectric property (also known as the Coulter method after the inventor of this device's basic principle), rapidly prompted further advances in cell counting instruments. The electrical-resistance-method-based technology allowed for analysis of cell sizes as well as cell numbers, hence mean RBC volume and hematocrit determination, making them reportable parameters. Concurrently, an improvement was added to the system to enable automated lysis and colorimetric analysis for quantification of hemoglobin in RBCs; further, by optimizing the lytic process, nucleus-size-based morphological WBC classification into lymphocytes, granulocytes, and others became possible (three-part WBC differential).

With various technological improvements incorporated into automated cell counter systems, it has become standard to analyze some morphological characteristics of cells and some clinical chemistry variables, beyond simple cell counting.

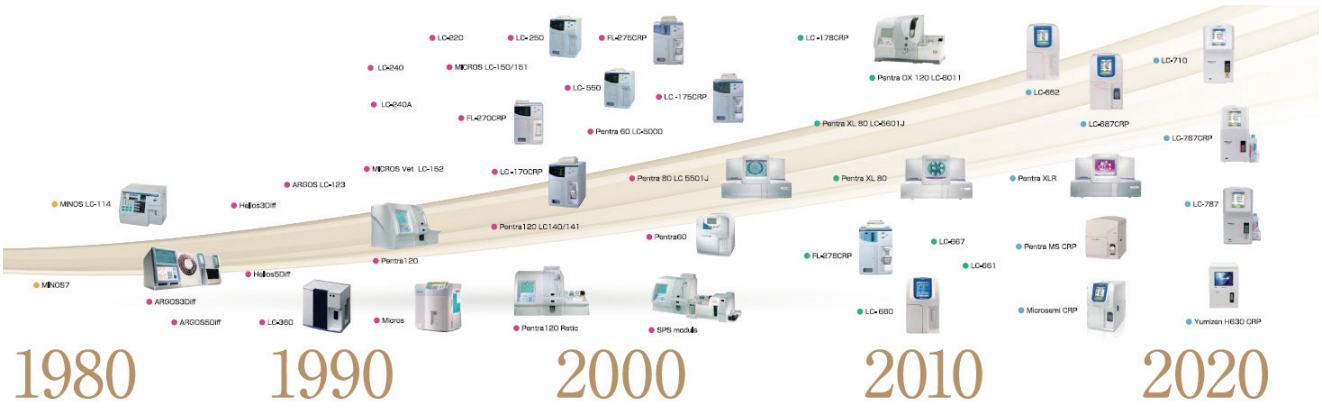
Along with the advancement in automated cell counters, their use further spread and their technological innovations progressed. With respect to WBC differentiation, which had remained a simplified classification, application of flow cytometry technology was promoted to enable a five-part differential as conducted by the manual microscopic approach. Manufactures attempted to produce hematology analyzers with distinctive features to achieve differentiation from competitors' devices, such as the addition of a screening flagging function for various hematological disorders.

Once the analysis technologies were established, the demand expanded, as a general trend, for improved operating efficiency based on fully automated hematology analysis and other laboratory workflow automation. The demand shifted from analysis-parameters- and test-performance-related aspects to solutions for higher operating efficiency, such as automated handling of large quantities of blood collection tubes (e.g., loading and unloading and post-analysis storage of analyzed samples) and within-hospital linkage of electronic patient records for smooth transition from testing to diagnosis and other in-hospital electronic information communication systems.

In parallel, smaller and simpler instruments are wanted so that hematology analysis that simply yields useful data for screening can be carried out with ease at primary care facilities, clinics and medical offices. This demand is described in the Point of Care section below.

## HORIBA's hematology business

The hematology analyzer business by HORIBA Ltd. dates back to 1996, when we acquired ABX S.A., a hematology analyzer manufacturer specialist of France. At that time, against the background of expanding demand for hematology analyzers, ABX was deploying




Note: The actual product launch year differs from the timing of regulatory certification. The time line is an idea based on Japan launch timing.

their business, focusing on compact analyzers for clinics, small hospitals, and small clinical laboratories to perform hematology analysis handily and readily. Figure 1 presents HORIBA Medical's hematology product portfolio in chronological order.

Of those, the three-part differential analyzers Micro Series and five-part differential analyzers Pentra Series have supported HORIBA Medical.

In earlier days, with the concept of micro-volume samples and small footprints, the Micro Series analyzers were deployed, mainly targeting countries having many clinics. In line with the market demand, HORIBA Medical launched an Open Tube model for flexible handling of sampling tubes and a Closed Tube model for analyzing samples in vacuum sampling tubes without the need for the operator to pierce the stoppers, which is expected to reduce the infection risk. HORIBA Medical also enhanced its computer software functions to support complicated day-to-day operation and data management at laboratories as the demand for such a tool grew greater.

For the past 30 years, the Micro Series has supported the brand image of HORIBA Medical's compact analyzers.

The Pentra Series incorporates two novel technological features as additional appealing points: the multi distribution sampling system (MDSS), a dilution method to enable analysis of samples available in micro quantities, and the double hydrodynamic sequential system (DHSS), which enables simultaneous optical and electrical analysis of the inner cell structure and cell volume of WBCs as they pass through a specified path at a controlled rate. The following Pentra Series systems are available: Pentra 60, which performs 60 tests per hour; Pentra 80 with an autoloader, which automatically loads sample tubes placed in the rack into the analyzer and performs 80 tests per hour; and Pentra 120, whose throughput was increased to 120 tests per hour to meet the demand for higher processing speed.

For devices installed at laboratories handling massive quantities of samples, enhanced ranges of precision control and data assurance are demanded. With its products such as peri analytical Pentra ML Data Management software and the slide preparation system (SPS), which automatically prepares samples subjected to final manual review, HORIBA Medical has continued to offer solutions to satisfy the need for automated analysis systems and also support for better system operation with higher efficiency.

The technology platforms of the Micro Series and the Pentra Series have continued to be fostered after ABX joined the HORIBA Group as a hematology specialist. In parallel, driven by technological collaboration with and transfer from Japan-based HORIBA Ltd., HORIBA Medical has acquired the engineering technology and know-how of Japan, achieving a synergistic effect leading to stable analysis system operation, especially in the field of compact analyzers. Of special note, however, is the deployment of an innovative product that was jointly developed by HORIBA Ltd. and HORIBA Medical based on the concept of simultaneous analysis of C-reactive protein (CRP) with other tests. Availability of WBC count together with another inflammation marker, CRP data on a compact analyzer, is highly beneficial in clinical settings, and this concept has long supported the HORIBA Medical product brand. Being particularly common among private practitioners and clinics, this system was in operation at over 10,000 facilities as of 2020 in Japan. While basically an automated hematology analyzer, this


Figure 2 HELO Solution initiatives and Yumizen H1500/H2500 Automation

system is actually used more often for POCT in close proximity to patients. More details are provided below.

Aiming to expand its business into the large hospital and central laboratory environment based on a record of over a decade of Pentra Series operation in the market, HORIBA Medical released its new concept, HORIBA Evolutive Laboratory Organization (HELO) Solution (Figure 2), with the new brand Yumizen established to support the concept.

Product and service lineups for the HELO Solution are to be gradually enhanced, including Yumizen H1500 and H2500, the main analyzers; Yumizen T6000, an automated conveyor system that connects these analyzers; and a management system thereof, Yumizen P8000.

Capitalizing on its technological expertise and experience nurtured on compact hematology analysis systems, HORIBA Medical aims to achieve further growth by expanding its compact analyzer business into the POCT field and providing more extensively comprehensive solutions with its large-sized analysis systems in line with the HELO Solution concept.

## Clinical Chemistry Field

### What is clinical chemistry?

Clinical chemistry analysis deals with body fluid (e.g., blood, urine) components, for example, glucose, cholesterol, proteins, and enzymes. Such analysis enables estimation of the health state, presence of diseases and other abnormalities, and nutritious status. Like hematology, clinical chemistry analysis is deemed to be essential as routine IVD testing.

### Clinical chemistry testing

Clinical chemistry analysis employs colorimetry in principle; namely, a color reaction resulting from an enzymatic interaction between the enzyme used and the target analyte is analyzed spectroscopically. Since body fluid components are present in abundance, their analyzers had been in as much, if not greater, demand as hematology analyzers and were introduced into clinical settings earlier than were hematology analysis systems. The basic flow of clinical chemistry testing is as follows: a body fluid sample harvested in a predetermined amount is subjected to a reaction (or reactions, depending on the analyte) with the designated reagent and then spectroscopic analysis, followed by washing as a post-treatment. The differentiation points for this analysis system lie in the speed, stability, and spectroscopy unit performance sufficient for mass processing of samples. On the other hand, wavelength characteristics differ between different manufacturers' spectroscopy units, yielding different reaction characteristics with each reagent used; that is, performance can vary depending on analysis system and reagent combinations. Data assurance and performance validation are therefore required for individual combinations. This is a feature of clinical chemistry analyzers that is not applicable to hematology analyzers.

Figure 3 Pentra C400

It is of note that, once a system of an automated analyzer was established, the demand grew for simultaneous multi-parameter analysis for varying intended purposes, which led to a broader range of parameters reportable on clinical chemistry analyzers, including electrolytes $Na^+$, $K^+$, and $Cl^-$. These electrolyte parameters are measured using not the above-mentioned enzyme method but the ion selective electrode (ISE) method. Despite this difference in analysis principle, many clinical chemistry analyzers commonly have an electrolyte analysis unit as an integrated module since electrolyte analysis can be performed using the same sample as that for other tests, and electrolyte analysis is frequently conducted for clinical purposes.

Parameters tested on the clinical chemistry analyzer employing not the enzymatic but immunological-reaction-based colorimetric or turbidimetric method are on the increase. This immunological parameter analysis often requires a specific system because of the difference in the reagents used and reactions involved; this field is established as immunoassay. Demand for this assay, which directly identifies proteins and other substances involved in metabolic reactions, is rapidly growing as a useful tool for highly specific diagnoses.

### HORIBA's clinical chemistry business

The clinical chemistry business of HORIBA started with the launch of Pentra 400 (Figure 3) in 1999. It was

just after ABX joined the HORIBA Group, and with solely hematology analyzer systems in the product lineup, concern about weak sales strategies was raised, prompting us to challenge clinical chemistry, another highly demanding field in the IVD market.

What is notable is that it was possible for us to apply the grating technology of Jobin Yvon Inc.—which joined the HORIBA Group at around the time of our entry into the clinical chemistry analyzers market—and the electrode technology developed by HORIBA of Japan to the spectrophotometer, an important analysis unit as described above. In particular, Jobin Yvon's grating technology is of a world-class high standard and is adopted in world-leading clinical chemistry devices.

Our clinical chemistry business started using instruments developed and manufactured by HORIBA and reagents supplied by our original equipment manufacturer (OEM), which was an existing reagent manufacturer, and we currently engage in sales of our products mainly in the U.S. and Southeast Asia. As in our hematology business, we are continuously adding to reagent items and updating our software products in response to user demand.

Our business in the U.S. has been especially stably expanding since 2009, and in line with the HELO deployment, we needed to develop a product lineup to offer to customers handling massive quantities of samples. We chose OEM collaboration with JEOL Ltd., which was seeking a footstep into the U.S. market at that time, over taking the risk of developing analyzers for mass processing of samples in-house, and we decided to deploy our business with a model called Yumizen C1200 in the U.S. After clearing the hurdles for U.S. market entry and fully preparing for the approval for our reagent items, we initiated sales of this analyzer in the U.S. in February 2021.

Meanwhile, in January 2021, HORIBA acquired MedTest Holdings, Inc. of the U.S., a company focusing on the manufacturing and sales of reagents for clinical chemistry analyzers. We thus brought technology and accumulated data on reagents for clinical chemistry analysis into the group, as we had long considered. We aim to further expand our IVD business, capitalizing on three development bases with different fields of specialization located in Japan, France, and the U.S.

## POCT Field

### What is POCT?

POCT refers to testing on the spot, as the name suggests. In the IVD field, in many cases analysis samples are collected at a single site and processed in mass there for higher efficiency, whereas POCT is performed in close proximity to the patient for prompt provision of care needed.

### Significance of POCT

One beneficial example is blood glucose measurement. Strict blood glucose control is required for patients undergoing treatment for diagnosed diabetes. They usually need to measure their fasting, preprandial, and postprandial blood glucose levels not only for disease status management but also for judgment for the need of insulin administration. Especially for the latter reason, it is imperative for patients to keep themselves informed of their own glucose levels to prevent life-threatening hypoglycemia from occurring.

Demand for testing that suggests on-the-spot management suited for each instance has been on the rise annually to address concerns for pharmacotherapy's side effects and decision making for prompt care needed in the event of an acute disease.

As the utility of POCT has become increasingly recognized, its risk has also come to be widely argued. For example, blood glucose measurements are affected by the timing at which the glucose level is measured (e.g.,

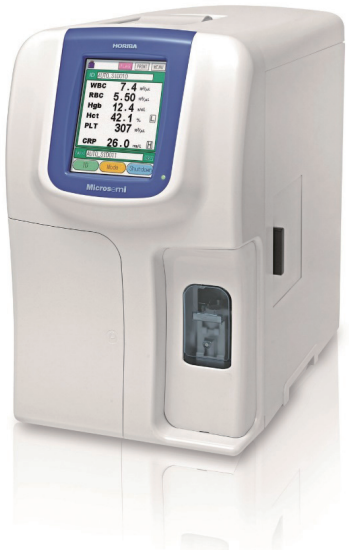



Figure 4 Microsemi CRP


Figure 5 HORIBA POCT Product: (Left) Yumizen M100 Banalyst, (Right) Antsense Duo

during fasting, before or after a meal) and by how it is measured (e.g., venous sampling, fingertip pricking, posture at the time of measurement). In the case of measurement on a clinical chemistry analyzer system at a laboratory, professional system management is required, including periodic maintenance for system behavioral assurance and routine precision control and calibration for assurance of obtained values. Namely, sample preparation and analyzer management should be undertaken by appropriately trained staff; however, such professionality may be compromised in POCT in exchange for quick test results, which then may lead to risk of medication misuse or misdiagnosis, as some argue.

To avoid such risks, many countries are preparing POCT practical guidelines and regulations on medical device handling. Because numerous diseases require prompt care, the demand for POCT will obviously grow further. However, POCT systems must be such that users are led to correct decisions; otherwise, confusion by misdiagnosis, or in the worst-case scenario, fatal consequences for patients could result. The growth of this field is deemed to depend on the promotion in tandem with regulations and standardization of POCT.

## HORIBA's POCT business

In the aforementioned hematology field, HORIBA Medical has proceeded with product deployment into POCT based on our compact analyzer expertise. Our core product in the POCT field is Micros CRP, an analyzer developed with an innovative concept of simultaneous CRP measurement.

WBC count and CRP levels are both known to fluctuate through the stages of the inflammatory response. WBCs promptly react to invading organisms at the injury site or via bacterial infection, while CRP is produced by hepatocytes in response to cytokines released in the immune reaction. WBCs and CRP thus differ in fluctuating timings and mechanisms, making these parameters useful in screening the inflammatory response at an early stage.

For instance, in the case of bacterial infection, WBCs increase rapidly in response to the invading bacteria, and then CRP levels begin to rise several hours later. In contrast, in the case of viral infection, it is not recognized as invasion by a foreign substance, resulting in negligeable changes in WBC and CRP levels. Antibiotic administration can lessen symptoms if they are caused by a bacterial invasion, but not those by a viral invasion. Yet, it is customary to give antibiotics in viral infection cases for the reason that a bacterial infection can occur or as a tentative measure. Recently, however, it is advised to avoid ungrounded antibiotic use because of the concern about the emergence of drug-resistant bacteria resulting from drug overuse. Simple screening has been shown to be useful in clinical settings.

Since WBC and CRP levels were separately measured on a hematology analyzer and a clinical chemistry analyzer, respectively, two types of samples (whole blood and plasma) were needed. Thus, analysis of this combination was cumbersome, although beneficial. Being a set of many tests run together as a panel, clinical chemistry used to be especially inconvenient for both reporting and utilization of test results for this combination. The novel technology enabling simultaneous WBC and CRP measurement in a single sample of whole blood got rid of the cumbersomeness and created an environment where simple analysis can be performed at appropriate timings. This simultaneous analysis system is considered to be an ideal tool for POCT operation.

The development of a product for simultaneous WBC and CRP assay accelerated our hematology analyzer development in Japan. The first renewed model of the Microsemi Series, customized in design and operability for the domestic general practitioners market, was launched in 2009 in Japan, and in 2013 an overseas model was launched abroad (Figure 4). The models for the domestic market were developed by incorporating the usability demanded by Japanese customers, as we learned from our past sales experience, in addition to performance and functional aspects. The improvements integrated into our analyzer systems, taking account of software and consumable exchange procedures, were also well accepted abroad, contributing greatly to our market expansion.

In Japan, since ABX joined the HORIBA Group, we have been exploring business deployment opportunities for products other than blood cell analyzers as well, setting our eyes on our POCT product portfolio augmentation. We inherited the business operations for the blood glucose meter model Antsense Series from Daikin Industries and Sankyo Co., Ltd. in 2000 and for the automated immunoassay analyzer Banalyst from Rohm Co., Ltd. in 2018 (Figure 5). There is not enough space for a detailed description of them herein, but they are products that will bring about the expansion of HORIBA Medical's product portfolio in the POCT field: Antsense Series as products that are expected to create synergy with the electrochemical and electrode technologies long possessed by HORIBA Ltd. as our core technologies, and Banalyst, a product which employs their original micro total analysis system (μTAS) technology, application of which is anticipated in more extensive areas.

## Closing remarks

HORIBA Medical shall continue to deploy products suitable for each field: hematology, on which we place emphasis, clinical chemistry, POCT, and although not described herein, coagulation. Furthermore, considering the shift in user needs from analysis itself to beyond analysis, we shall proceed with studies for solutions to offer our customers new added value, such as proposals for academic applications, data linkage via the Internet of Things, and services for supporting compliance with the relevant regulatory requirements.

Medical devices are strictly regulated by laws and regulations as important areas protecting people's health and lives. The manufacturers of such devices are responsible for applying a quality management system across the board, not limited to the validity and utility of the device performance. As a healthcare provider, we commit ourselves to user safety and security by abiding by the regulations while offering novel functions, good performance, and services. It is HORIBA Medical's mission to continuously contribute to medicine, healthcare, and patients' better quality of life through analysis operations.

* Editorial note: This content is based on HORIBA's investigation at the year of issue unless otherwise stated.

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