The Business Trend of In-Vitro Diagnostics: MAST CLA and Seratestam

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Antigen-antibody and enzyme reactions are basic technologies used for in-vitro diagnostics. The antigen-antibody reaction has high sensitivity and measurement specificity; for example, the concentration of pg/mL is expected as a detection limit. The enzyme reaction technology enables rapid measurement based on a simple principle, which also means the design of the instrument can be kept simple. Medical Business Unit of Hitachi Chemical is developing allergy and POCT (Point-of-Care Testing) businesses as two cores. We are currently marketing the Mastimmunosystems ("MAST CLA") for the allergy business and Seratestam for the POCT business respectively. MAST CLA is an immunological diagnostic capable of measuring 33 allergens simultaneously with 200 µL of serum. Seratestam is a biochemical diagnostic capable of measuring 22 items with information on a two-dimensional bar code, which records measurement parameters etc. A skilled laboratory technician is not needed to operate the Seratestam. The current business of in-vitro diagnostics is aligned to the trend among patients for QOL (Quality of Life) improvement. The future goal is to expand sales of current products and become a company that spreads diagnostic reagents, not only domestically, in Europe and the America but worldwide within the next 20 years.

1 Diagnostic Reagent

Diagnostic reagents can be classified into two categories, namely in-vivo diagnostics that are directly administered to the human body and in-vitro diagnostics that analyze components in blood, urine, etc. Although both diagnostics can be effective auxiliary methods of diagnosing diseases, Hitachi Chemical lines up only in-vitro diagnostic reagents for our products and our R&D activity is dedicated to in in-vitro diagnostic reagents only.

Japan's Pharmaceutical Affairs Law defines a diagnostic reagent as a "medicinal product not administered directly to humans or animals of medicinal products used solely to diagnose diseases". Accordingly, diagnostic reagents are legally classified as medicinal products and strict rules must be observed when developing, manufacturing and controlling the same. Our medical business unit abides by these rules and laws, having obtained international standard certification (ISO 13485) in 2005 as well as a license granted under Japan's Pharmaceutical Affairs Law.

2 Technology Used for Diagnostic Reagents

Diagnostic reagents are required to measure trace components accurately. The most basic elemental technology enabling this is a technology based on an antigen-antibody reaction. For instance, if the human body is infected with bacteria, it produces an antibody and by measuring this antibody, we can indirectly determine whether it is infected or not. When developing diagnostic reagents, we built an antigen-based measurement system (in this case, protein derived from bacteria) as a material that reacts specifically with the targeted antibody for measurement. Conversely, if we want to measure a specific substance in-vivo, we prepare an antibody in advance that reacts specifically with the targeted substance for measurement and use it as testing material. Since the sensitivity and specificity of the antigen-antibody reaction is very high; as an example of sensitivity, concentration at a level of pg/mL can be measured.

Conversely, another measurement system uses specific enzyme and substrate reactions. For instance, when measuring enzymatic activity in-vivo, one method uses an enzyme-specific substrate. Although the sensitivity of this method is not as high as that of antigen-antibody reactions, the measurement process simply requires mixing of enzyme and substrate, hence does not take long. Moreover, the progress of the reaction is accompanied by color changes, meaning a spectrophotometer suffices as a detector and allowing simplified design of the measurement instrument.

Other elemental technologies include PCR (Polymerase Chain Reaction), which is a method of amplifying genes (DNA segments) that can detect minute amounts of genes and is mainly used for assays of bacteria and viruses.

3 Market and Trends of Diagnostic Reagents

The main market segment for diagnostic reagents in Japan is that for testing infectious diseases: 60 billion yen annually, followed by immunological investigations (tests using immune responses, e.g. allergy tests) and biochemical examinations (measuring levels of enzymes, lipids and electrolytes inside the body e.g. liver function test): at 56 billion yen each and tumor markers at 23 billion yen annually. (Statistics 2010, Japan Association of Clinical Reagents Industries)

In recent years, the POCT market has been expanding rapidly, already reaching USD 90 billion in the U.S. and exceeding 100 billion yen in Japan.

POCT is a collective term for tests performed near patients e.g. at the office of medical practitioner. It is attracting attention as a test which helps enhance the quality of diagnoses as clinicians can judge and give patients medical attention promptly based on test results, give follow-up observations and monitor patients' prognosis.

4 Diagnostic Reagents of Hitachi Chemical

Medical Business Unit is involved in allergy and POCT businesses as two key sectors. The former lines up allergy diagnostic reagents and MAST CLA as core products; the latter currently lines up 22 items as Seratestam.

4.1 The Mastimmunosystems ("MAST CLA")

MAST CLA is a diagnostic reagent used to investigate allergy by measuring the IgE antibody in serum (**Figure 1**). Allergy and IgE are closely related; for example, a specific IgE to the cedar allergen can be found in the serum of a patient with the pollen allergy.

The most remarkable feature of MAST CLA is the capability to test 33 items of an allergen-specific IgE simultaneously. 33 types of allergen are immobilized in the solid phase of a specialized reaction container, whereupon an allergy test is completed about 6 hours after the serum is dispensed[1)].

The measurement principle is shown in **Figure 2**. The first step involves reacting the allergen that is immobilized in the solid phase and the allergen-specific IgE in serum. The second step is to react the enzyme labeled anti-human IgE antibody to form a complex of "allergen"-"specific IgE"-"enzyme labeled antibody". Finally, dispense luminescent reagent (luminol, hydrogen peroxide) and measure the degree of luminescence using a specialized Luminometer.

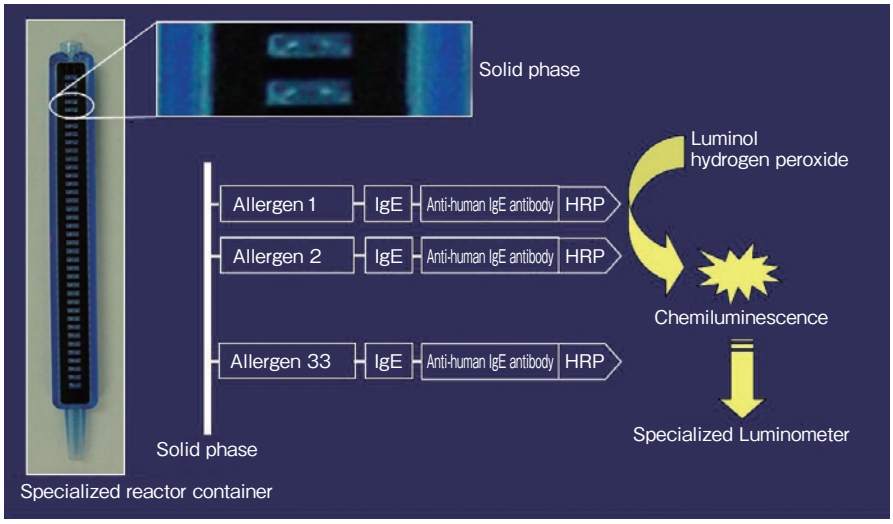
MAST CLA uses the 33 types of allergen listed in **Table 1**. Because extraction and purification methods differ for each of the 33 allergen types and the immobilization methods vary, MAST CLA preparation requires numerous technologies and know-how. We also have full-filling serum libraries that are essential for product development, quality maintenance and which offer us a major advantage when operating the allergy business.

MAST CLA has another feature-namely that a mere 200 µL of serum suffices to measure 33 items. This is especially advantageous for measurement in infants as the volume of blood required for sampling is very limited. We envision the development of new reagents used for additional items targeted at certain medical departments for diagnosis and treatment e.g. pediatrics.

Figure 1 The Components of MAST CLA
(Left : Luminometer; Specialized Measurement Instrument
Right : Reagents)

Table 1 The Measurement Items of MAST CLA

No.	Test Item Name	No.	Test Item Name
1	Mite f	18	Aspergillus
2	House Dust	19	Latex
3	Cat Dander	20	Buckwheat
4	Dog Dander	21	Wheat
5	Timothy Grass	22	Peanut
6	Sweet Vernal	23	Soybean
7	Orchard Grass	24	Rice
8	Ragweed Mix	25	Tuna
9	Mugwort	26	Salmon
10	Japanese Cedar	27	Shrimp
11	Japanese Cypress	28	Crab
12	Black Alder	29	Cheddar Cheese
13	White Birch	30	Milk
14	Penicillium	31	Beef
15	Cladosporium	32	Chicken
16	Candida	33	Egg White
17	Alternaria		



HRP : Horseradish Peroxidase

Figure 2 The MAST CLA Measurement Principle

4.2 Seratestam

Seratestam can currently be used to measure 22 test items, basically in the biochemical field in Japan (**Table 2**). Eight of the 22 test items are listed as key measurement items for "special health checkups" and "special health guidance" as set forth by law, allowing clinicians to obtain critical information to diagnose lifestyle-related diseases.

Another feature of Seratestam is its compatibility with large analyzers as it uses the same liquid reagents used for large automated analyzers and is easy to handle as it is filled in specialized compact cartridges. Also, a 2D bar code is labeled on cartridges and once a sample and diagnostic reagent are set up in the clinical analyzer, testing starts as soon as the 2D bar code is automatically read, eliminating the need for an experienced laboratory technician to operate the clinical analyzer (**Figure 3**).

One example of the measurement principles is given in **Figure 4**. Here, the first step is to dispense serum into a reaction cell, followed by pouring the diluent into the reaction cell and diluting the serum. Next, the reagent that reacts with the target substance in the serum is dispensed into the same reaction cell and the absorbance that increases (or decreases) in proportion to the concentration of the target substance is measured. The measuring time required is about 15 minutes. Seratestam is designed to ensure effective mixing of diagnostic reagents, even if mechanical stirring is not separately available, meaning measuring equipment can be kept simple.

Since the 2D bar code records measuring and calibration parameters, etc., the operator need not configure parameters him/herself, can skip calibrations and keep operations simple. Although the majority of measurement items are currently biochemical-related, sales of Seratestam have already started in Europe and we are preparing to launch sales in the U.S.; three electrolytes - Na, K and Cl - have been newly developed and lined up.

Table 2 The Measurement Items of Seratestam

No.	Name of Item	
1	ALP	Enzyme
2	γ -GTP	
3	LD	
4	GOT/AST	
5	GPT/ALT	
6	AMY	
7	CK	
8	GLU	Blood sugar and lipid
9	TG	
10	T-CHO	
11	HbA1c	
12	HDL-C	
13	LDL-C	
14	CRE	Protein including nitrogen
15	BIL	
16	BUN	
17	UA	
18	TP	
19	ALB	
20	CRP	
21	CA	Electrolyte
22	IP	

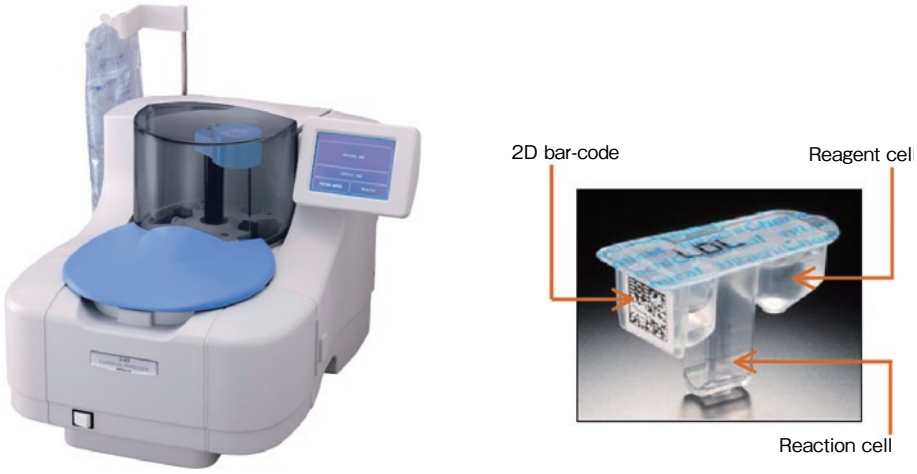


Figure 3 The Components of Seratestam
(Left : Clinical Analyzer; Specialized Full-Automatic Analyzer Right: Reagents)

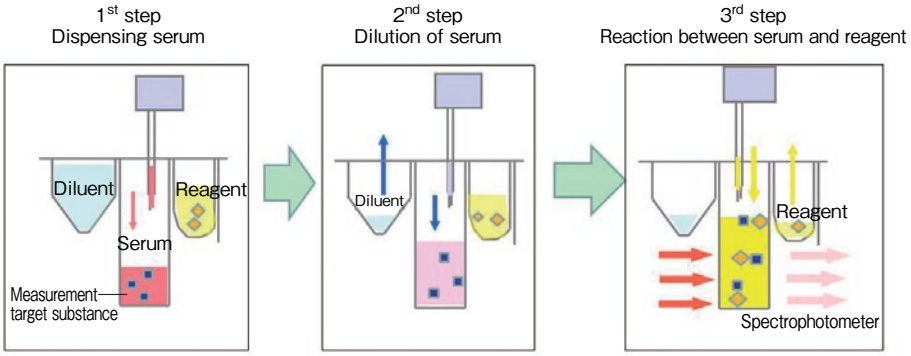


Figure 4 The Measurement Principle for Seratestam

5 Diagnostic Businesses to Come 20 Years After

The improvement of QOL will be a keyword for medical service in future. The early discovery and confirmation of disease is considered increasingly crucial and further enhanced basic performance parameters e.g. sensitivity, specificity and speed will be required.

Today, diagnostic reagents are used as one of the options to identify illness. Soon, however, healthy individuals may self-administer their own health. If a preventive health check function is added to diagnostic reagents, we expect a new market to emerge. Henceforth, tailor-made medical services may become important. Once each home is linked online to healthcare providers, patients can receive measurement results and medical practice at home.

Hitachi Chemical is pondering the next actions to meet the needs for QOL improvement in patients. In the allergy business sector, we plan to develop a fully-automated instrument for MAST CLA and market it worldwide while running the current business model built on clinical laboratories. Currently MAST CLA can measure IgE in blood. Subsequently, we will challenge the next allergy diagnosis, including measurement of sample in urine and saliva by substantially enhancing reagent sensitivity.

In the POCT field, we plan to develop and expand unique measurement items, mainly targeting lifestyle-related diseases. Although Seratestam currently measures only biochemical measurement items, we plan to add immunological measurement items, downsize the Seratestam clinical analyzer and target rapid testing. We hope to develop a compact Seratestam clinical analyzer suitable for home-use and enter a new market of preventive diagnostics with appropriate specifications usable for individual health control.

In 20 years, we will become a company operating diagnostic reagent businesses not only in Japan, Europe and the United States but also globally, by expanding the sales of current product lines.

【References】

1) Takeshi Sawazaki et al., Hitachi Review 86, p. 749 (2004)