EXPORT OPPORTUNITIES IN JAPAN

THE DIAGNOSTICS MARKET

External Affairs and International Trade Canada

Canada

THE DIAGNOSTICS MARKET

This is an unedited translation of a Japanese study on the diagnostics industry in Japan.

by

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JAPAN

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La présente étude, réalisée au Japon et fondée sur un rapport publié en japonais, est destinée à communiquer des données scientifiques sur les technniques de pointe en matière de diagnostic à un nombre très restreint de spécialistes. Par conséquent, en raison de sa diffusion extrêmement restreinte et conformément aux directives contenues dans la circulaire administrative 17/87 (ADL) d'Affaires extérieures et Commerce extérieur Canada sur les publications et les langues officielles, cette étude est publiée en anglais seulement.

Preface

Canadian exporters are discovering a new Japan. Firms which have focussed their efforts on specific target market segments have seen their results soar. Their success bears witness to important changes which have recently occurred in the Japanese market.

Since the mid 1980s, the substantial appreciation of the yen, Japan's concerted policy of domestic demand stimulation and a shift towards a more open import regime have significantly enhanced the competitiveness of Canadian goods in the Japanese market. Specific opportunities have emerged in areas previously closed to foreign suppliers.

This "Export Opportunities in Japan" series is published by External Affairs and International Trade Canada to assist Canadian exporters in seizing these exciting new opportunities. It pinpoints specific market segments where new Japanese import demand meets proven Canadian capability. It includes market segment profiles, details specific market technical characteristics, documents success stories and provides market bibliographies and key contact lists.

The series is designed not only as a reference and guide but also as the basis for future joint marketing action by Canadian firms, their trade associations and Canadian government departments. The series has been produced in consultation with the Japanese Export Trade Organization (JETRO) and has the support of the Japanese Ministry of International Trade and Industry (MITI).

Further information and guidance is available from:

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The Canadian Embassy in Japan has made important contributions to this series of market studies. Additional assistance and information is available from the Embassy in Tokyo.

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1-1) Summary of Japanese Market

1) The Japanese market for in-vitro diagnostic drugs is 200 billion yen or slightly less (manufacturer shipping costs) and approximately 200 companies have entered this market. Of these, 162 companies are members of the Japan Association of Reagents for Clinical Laboratory Tests (corporation financed by individual companies; the association was formed for the sound development of the industry and for connections between each industry and to open a window of communication with the Ministry of Health and Welfare).

2) There are five main entry fields in terms of their business conditions.

A) special manufacturers: companies that started from industrial reagents and have expanded to the field of clinical test reagents, company that entered the same field from the start, etc.
Examples: Wako Pure Chemical, Eiken Chemical, Sanko Junyaku, etc.

B) Drug manufacturers: diagnostic drug industry was developed as a business related to drugs.
Examples: Sankyo, Shionogi, Chugai Pharmaceutical, etc.

C) Industrial manufacturers: participants from different fields, such as chemistry, food, analytical instrument etc.
Examples: Tosoh, Fuji Film, Toyobo, Hitachi Chemical, etc.

D) Foreign manufacturers: participants from foreign countries, mergers with Japanese company, etc.
Examples: Dainabot, Dupont Japan, Nippon Roche, Hoechst Japan, BMY, Pharmacia, etc.

E) Others: business developments from commercial laboratories to manufacturing and, companies not previously listed
Examples: S. R. L., BM. Laboratory, Otsuka Assay Research Laboratory, etc.

Of the aforementioned, the trend in the last several years has been activity from entry of participants from different fields and foreign companies. In particular, there will be a demand for high technical and development capability with the sudden progress made in diagnostic technology in recent years and participants from companies that are backed by a large amount of capital will play a role.

3) Reorganization of the Industry

Many companies participate in a small market, as previously explained, and small companies survive and inevitably die with the progress made in technological centralization. The following are examples of industries that have a major impact on the field of diagnostic drugs:

Companies with annual sales over 10 billion yen

1. Dainabot
2. Eiken Chemical
3. Fujirebio
4. Wako Pure Chemical

Companies with annual sales of 6 - 10 billion yen

5. International Reagents
6. Miles-Sankyo
7. Daiichi Radioisotope Laboratories
8. Dia-Iatron
9. Ono Yakuhin
10. Sankyo

The majority of companies belong to the group of companies with sales of one billion yen or less.

Consequently, the following points are essential for survival in the future.

Companies with development capability

High technological development capability is essential. Development capability emphasizing new assay systems, such as DNA probe diagnosis, chemical luminescence, etc., is essential.

Companies with capital power

Companies themselves must be able to survive conditions such as fierce development and share competition from each company, stock wars, etc. Even with recent technological introductions and cooperation in joint development, as much capital as 1 or 2 billion yen is needed. Several billion yen may be needed for commercialization.

Companies with Selling Power

Of course, the top manufacturers have strong selling power. There is intense rivalry in price wars, particularly in commercial laboratories. Selling power backed by total services is essential.

The aforementioned are the factors that are particularly important. Two or 3 examples of recent trends will be given.

Companies with Development Capability

Fujirebio: Progress was made in screening of 8,000,000 items per test at the Nisseki Blood Center using diagnostic drugs for the ELISA method initially made by Dainabot. However, this was replaced with a diagnostic drug developed by Fujirebio using agglutination method. It was confirmed that in 1989, the market including that in general hospitals had exceeded 1.3 billion yen.

The same company has developed a diagnostic drug for agglutination for ATL and has obtained good results.

Companies with Capital Power

Chugai Pharmaceutical: This is related to the development capability in the above example. However, this is a case where the technology is not that of this company, but rather technology that was borrowed from another company. The same company paid approximately $100 million to the venture business of Gene Probe Co. of the U.S.

The actual results follow. The Gene Probe Co. was at the top of the world market with its DNA probe diagnostic technology. Other companies were surprised at the fact that Chugai Pharmaceutical had obtained this technology. M & A in this industry has been recently started because of the capital power of Chugai.

Companies with Selling Power

Sanko Junyaku: On an industrial scale, this manufacturer is next to the top manufacturers (this company started from a specialized trading company and is now aiming toward manufacturing). Its industrial selling power is publicly acknowledged. It is a particularly popular business for new entry manufacturers from different industries, etc. It has recently started to handle IgERAST EIA (Japan DPC product), which is receiving considerable industrial attention.

The aforementioned are actual examples. However, it does appear that cooperation (capital, technological, etc.) with other companies, serialization and reorganization of industries, such as M & A., etc., will proceeded in the future in order to compensate for week points and inadequacies while combining the characteristics and unique features of each company of the same field.

1-2) Market size and structure

The market size of diagnostics in Japan is described in Appendix 1-1) and 1-2) with a breakdown into 7 test fields; general test, haematological test, biochemical test, immunoserological test, RIA (in-vitro), microbiological test and control. The definition of each test is also described in Appendix 1-1).

Market structure is illustrated in Appendix 1-3) with estimates based upon national medical expenses.

2. Market Trends

2-1) Major test items

30 major test items are listed in Appendix 2-1. Ten major items are CEA, Syphilis, HBs antigen, AFP, Total cholesterol, Triglyceride, CA19-9, HD cholesterol, Amylase and ASO. Thirty major items hold 43.8% of the market and amounted to 78 billion yen in 1989. Such items as CA19-9 and ATL show a rapid growth in sales with a more than 10% annual increase.

General tendency of the market is as follows:

1) Correlation Between Treatment and Clinical tests

The purpose of clinical tests is to play a role in treatment by diagnosis of the disease. However, depending on the test item, the test may not play a direct role in treatment.

An actual example is tumor markers which have a broad market. Their original purpose was to aid in early diagnosis. However, most tumor markers are not useful unless the disease is in its final stages and therefore, tumor markers are clinically significant for prognosis monitoring after treatment.

Moreover, there are no test items for infectious diseases, which is a large market, whose purpose is treatment. They are used for confirmation after treatment and to test transfusions and check for mother-child infections. This is due to a problem with the current test methods. Cultivation in the case of microbiology takes at least 2 to 3 days. Antibiotic is generally administered before identifying the bacteria. The main tests for viral infections are antigen tests and therefore, antibody titers are not obtained unless the tests are performed at least 2 weeks after infection. Moreover, thus far there are no drugs for treatment of viral infections.

Therefore, attention is being focused in microbiology on direct kits with which cultivation is not necessary and on antigen tests with which checking is possible immediately after viral infection.

Moreover, as with liver function tests, there are too many items that are used as indices and attempts are now being made to limit test items to those that play a role in this field.

Tests are supervised by doctors and it is necessary for the doctor to know the correlation between the extent and type of illness and test items and to be able to read data and make a diagnosis. Therefore, in this sense, there is a difference in terms of the appropriate level. Consequently, coagulation tests, etc., are still classified as special tests because of the low level of knowledge of doctors.

2) Test System

Systems in test laboratories in hospitals vary with each facility. However, in general, test laboratories in hospitals of 50 beds to 300 beds do all tests regardless of test field.

In hospitals of 400 beds or more, there is a central test division, which is divided into sections by each test field. These sections are classified as general tests, haematology, biochemistry, immune serum test, microbiology, and pathology sections.

RIA (in-vitro) is often the same section as RIA (in-vivo) and roentgen and it is often included in the nuclear medicine laboratory and radiology.

Moreover, tests of transfusion, drugs, etc., are performed as needed in large hospitals (500 beds or more).

There are many cases where general tests are performed on an outpatient basis, and there may even be an outpatient test laboratory.

There are also hospitals where only emergency tests, such as blood counts in haematology, blood sugar, Na, K, Cl, and CPK in biochemistry, TDM in immune serum test, etc., are performed and there are emergency test laboratories, etc.

The aforementioned is the current condition, but future trends include changes with development of new determination theories and automation.

Actually, there are also cases where microbiology, fecal occult blood of general tests, blood coagulation tests, etc., are performed in immune serum test laboratories with the development of new determination methods that use antigen-antibody reactions.

Moreover, some immune serum items are being changed to biochemistry items with automation of immunoserological tests.

In addition, although profits have increased with treatment of large amounts of specimens by centralization of specimens in central test divisions, it has been difficult to analyze specimens in emergencies in these cases. Moreover, since each section is specialized, there has been a reduction in the importance of tests that fall into a boundary category and in the number of meaningless tests because of unprofitable sections have been eliminated and because of determination of the same item in more than one field.

Therefore, attention is being focused on outpatient tests and on bedside tests by simplified tests as a countermeasure for eliminating these tests from conventional central tests.

3) Automation

The progress made in automation varies with each test field and the conditions by each test field are shown below:

The degree of completion of automation of urinalyses, which account for the majority of the market for general tests, is high with the development of small desktop type devices for outpatient use and large devices for central tests. Moreover, these devices have become popular.

The degree of completion of automation of blood cell counters that count blood cells in haematology is high with the development of large and small devices. These devices have also become popular. The degree of completion of automation of blood automatic classification devices that automatically give hemograms is high. However, since the cost is high at approximately 30,000,000 yen, it is only popular in large hospitals with 500 beds or more. Test of blood coagulation is a special test itself and coagulometers are of low popularity. However, progress has been made in semi-automation of coagulometers from manual types.

Of the clinical test fields, biochemistry is the most automated field. This centers on automated chemical analysis devices. It is the first anniversary of the super-multi-type for treatment of large amounts of specimen and the current main trends in automated analysis devices are single multi-types and random-access types for use in small and medium sized hospitals.

Moreover, attention is no being focused on dry chemistry systems targeting outpatient tests, overnight tests, emergency tests, doctors in private practice and hospitals with 20 to 50 beds.

With regard to immunoserological tests, automation emphasizing plasma proteins has been completed in the field of low sensitivity at a cut-off level of ug/ml to several ten ng/ml. EIA, FIA, CLIA, etc., have been developed for fields of high sensitivity of several ng/ml to several pg/ml. EIA is the most automated of these fields, but there are not predictions as to what the main assay system will be.

Automation has been the slowest in the field of microbiology. There are automatic microbiological test devices that automate sensitivity tests. However, the cost is high at 20,000,000 yen and these devices are of low popularity because unless they are used in large hospitals with many specimens, profits are low.

The market for RIA (in-vitro) is limited to large hospitals and test centers. Therefore, it can be said that automation has become popular for auto-well counters.

The aforementioned is the state of automation in each test field. Problem points include the price reduction of 50% or more in list price focusing on automated chemical analysis devices for biochemistry, and restriction of hard markets with progress in leasing of equipment emphasizing immunoassay (immune serum test).

4) High-speed, simplified tests

Progress will be made in the future on high-speed, simplified tests from the points of tests that are directly tied to treatment and service to patients.

The state of progress to meet these needs varies with each test field. These needs have almost been met in terms of general tests and haematology. Since RIA (in-vitro) involves many special test items and from the point of determination theory, there are limits to making these tests high speed and simple, future trends will be emphasis on biochemistry, immunoassay, and microbiology.

In biochemistry, simple analytical systems and dry chemistry systems are high-speed and simplified. Inexpensive reagent unit costs for automated chemical analysis and spectrophotometers in large hospitals and higher profits with outpatient tests for test centers than in large and medium-sized hospitals and private practices are problem points.

In immunoassay, pregnancy diagnostic drugs are popular, but future demands will be for viral antigen tests. In particular, there is a need for check for mother-child infections by herpes and chlamydia where expansion of the market is anticipated. There is also a demand for checks for other mother-child infections and transfusion checks. The need for simple kits for HBs antigen, ATL antibody, HIV antibody, rubella antibody, toxo antibody, syphilis, etc., is also high. However, since there are no methods for curing viral infections, there is little chance of a market forming for curing viral infections in the short run.

There are high-speed simple kits for microbiological tests of group A streptococcus, C D bacteria, etc., but it has been concluded that these do not meet the working schedule for isolation, cultivation and identification in microbiology laboratories and that tests are impossible on an outpatient basis because it takes as long as 10 minutes to collect specimens and evaluate the findings. Therefore, these are not popular.

Moreover, attention is being focused on DNA probe methods as high-speed kits for bacteria and virus. However, at the present time there are few items on the market and use of these items is complicated. Therefore, it will take time for a market for these kits to form.

2-2) Trends in selected items: tumor markers, diabetes, liver & kidney disease

The following items are selected in terms of market growth and adoption of new test methods. Market information such as market size is mentioned in Appendices 2-2) to 2-4).

Test items	Purpose of test and subject diseases	Determination method	Use of kits	Insurance score
A. Tumor Markers				
A-1. KMO-1	Diagnosis of cancer of the pancreas, bile ducts, liver	EIA, RPHA	yes	RPHA = 80 EIA = 300
A-2. CA-50	Diagnosis of cancer of the pancreas, bile ducts, liver Combination assay of CA19-9	EIA FIA	yes	300
A-3. ST439	Diagnosis of cancer of the breast, pancreas, gall bladder, liver, large intestines	EIA	yes	250
A-4. BFP	Diagnosis of cancer of the stomach and large intestines, urinary bladder, and ovaries	EIA	yes	300
A-5. DUPAN-2	The positive rate of cancer of the pancreas, gall bladder, and liver is high. Effective for cancer of the ovaries, large intestines, breast, etc	EIA	yes	250
A-6. SLX	Pulmonary adenoma, lung cancer, pancreatic cancer, ovarian cancer	RIA	yes	400
A-7. TPA	Each type of tumor marker (common antigen), indicator of degree of activity of tumor, clinical monitor	RIA	yes	250
A-8. SCC antigen	Squamous cell carcinoma, particularly effective for diagnosis of cervical squamous cell carcinoma	RIA	yes	300
A-9. NSE	Diagnosis of small cell carcinoma of the lungs, etc.	EIA, RIA	yes	400
A-10. CA19-9	Diagnosis of each type of cancer, positive rate is particularly high for pancreatic cancer and acute pancreatitis. Effective as a monitor for clinical effects and recurrence.	EIA, RIA	yes	300
A-11. CA125	Diagnosis of ovarian cancer and pancreatic cancer.	EIA, RIA	yes	400
A-12. CA15-3	Diagnosis of breast cancer	RIA	yes	300
A-13. IAP	Screening for cancer in general	SRID immune turbidimetry	yes	100

Test items	Purpose of test and subject diseases	Determination method	Use of kits	Insurance score
A-14. Sm	Diagnosis of cancer of the prostate.	EIA	yes	450
A-15. Estrase 1	Screening for pancreatic disorders and pancreatic cancer.	RIA	yes	300
A-16. PGR	Index for treatment of breast cancer	EIA	yes	700
B. Diabetes Test				
B-1. hemo-globin A1	Blood sugar control for diabetes (past 2 to 3 months)	Electro-phoresis Mini-column, affinity column	yes	80
B-2 hemo-globin A1c	Blood sugar control for diabetes (past 2 to 3 months)	EPLC, affinity column, etc.	yes	110
B-3 urinary albumin	Early diagnosis of diabetic kidney disease	RIA, immune turbidity latex	yes	200
B-4 fruct-osamine	Indicator for blood sugar control for diabetes	Colorimetry	yes	60
B-5 1.5-AG	Indicator for blood sugar control for diabetes	Column method	no	no
C. Liver Disease				
C-1 guan-ase	Diagnosis of liver disease	Colorimetry	yes	80
C-2 ADA	Diagnosis of liver disease	Column method	yes	80
C-3 LCAT	Liver and lipid metabolism anomalies	Colorimetry	yes	150
C-4 HCV	Diagnosis of HCV	UV method	yes	250
D. Kidney Disease				
D-1 NAG	Diagnosis of kidney disease	Colorimetry	yes	80
D-2 AAP	Diagnosis of kidney disease (renal cancer, glomerular nephritis, etc.)	Colorimetry	yes	20

Test items	Purpose of test and subject diseases	Determination method	Use of kits	Insurance score
E. Others				
E-1 immune complex	Diagnosis of auto-immune disease	EIA,	yes	350
E-2 interferon (gamma)	Resistance to cell necrosis (beta) Antitumor properties of cells	RIA, EIA	yes	no
E-3 interleukin	Diagnosis of inflammatory reactions, infectious disease	EIA	yes	no

Overview of each market can be summarized as follows:

A. Tumor Markers

CEA and AFP are the two major items with long-standing substantial market share. Beta2-microglobulin and ferritin have followed them and in 1985 CA19-9 entered into the dramatically expanding market. Tumor markers are usually applied for screening and monitoring after treatment as a combination assay. For example, in the case of a test for pancreas cancer, diagnosis accuracy can be enhanced by the combination of three test items, CEA, CA19-9 and KMO-1. It is the same for the monitoring of after-treatment. It is not sufficient to test with a single marker. Thus, the diagnostics market has been expanded by the increase in the number of tests which enables the application of a combination of two or more test items. This indicates that there are few markers having very high accuracy.

The revision of health insurance scores to be implemented from April 1990 (refer to Appendix 3-1) will have an adverse effect on this market. There has been no restriction of invoicing of insurance scores in the past, but invoicing can be made only once for screening test and only monthly base invoice is allowed for monitoring test. Therefore, it is most likely that combination assays will not be conducted for monitoring. This may reduce the demand of tumor markers.

B. Diabetes

It is estimated that there are 2.5 to 3 million diabetes patients in Japan. Among them, approximately 200,000 people take insulin. The major test item has been blood sugar and promising markers such as haemoglobin A1, haemoglobin A1C, urine albumin and fructosamine have appeared on the market. Thus, the market is growing. Self-testing of blood sugar at home is also being expanded.

C. Liver Disease

Such test items as guanase, ADA and LCAT are recently gathering attention in the market. Also, HCV is expected as a promising item. Ortho Diagnostic Systems has started marketing an ELISA kit for HCV in Japan. It is expected that 12 million tests will be conducted by this kit in 1990. Eiken Chemical plans to start marketing HCV diagnostics this year.

D. Kidney Disease

Few test items are expected to be growing except for NAG and AAP.

E. Others

Immune complex, interleukin and interferon are promising items, although these items are more or less for R & D purposes. However, the health insurance score (350) for immune complex was approved in January 1990, which will enlarge the market.

The current situation and development points are as follows:

A. Items related to tumor markers

Test items	Determination method	Current state	Problems, trends in development
A-1. KMO-1	EIA RPHA	Washed twice in 2 steps with EIA, micro-plate method	Improved to 1 step method
A-2. CA-50	EIA beads FIA	Cut-off level of 40 U/ml. There are two washing steps that are somewhat complicated. Semi-automated type.	Pharmacia markets on FIA kit
A-3. ST439	EIA	Automation is a problem with EIA bead method.	Nihon Kayaku
A-4. BFP	EIA	Use of serum as the specimen, use of urine as the specimen, or use of both as the target are problems.	Nihon Kayaku '90 sales anticipated
A-5. DUPAN-2	EIA Micro-plates	Cut-off level of 150 U/ml. Corona electrical device has reader with concentration-conversion ROM	Being prepared for expansion of indications and treatment with markers for gall bladder diseases (Kyowa Medex)
A-6. SLX	RIA	RIA bead method	Development of NON-RIA method is a problem.
A-7. TPA	RIA	Cut-off level of 100 U/ml. Improved from conventional devices in terms of ease of use and reproducibility. Determination time is curtailed from 3 days to 1 day.	TPA drafting know-how is difficult and there is little prospect for new entries.
A-8. SCC antigen	RIA beads	Improved control and sensitivity and curtailed determination time with use of monoclonal antibody when compared to conventional double antibody method. Also improved in that there is only one washing.	EIA development (Dainabot)
A-9. NSE	RIA double antibody method EIA Sandwich method	RIA is a double antibody method and therefore, the procedure is somewhat complicated. EIA used polyethylene beads.	Eiken plans to market EIA in June of 1988
A-10 CA19-9	RIA EIA	Mainly RIA. EIA is very difficult to fully automate because it uses the bead method.	Development is necessary for EIA to be the main trend in terms of future popularity.

Test items	Determination method	Current state	Problems, trends in development
A-11. CA125	RIA	Mainly RIA	Increasing use of EIA is necessary for future popularity
A-12. CA15-3	RIA	Mainly RIA	Fuji Rebio plans to market EIA
A-13. IAP	SRID Immune turbidity method	Cut off level is 500 ug/ml (for both methods). Immune turbidity is marketed and therefore, automation is proceeding.	A reduction in insurance score is anticipated because of automation. It is currently 100 points.
A-14. gamma-Sm	EIA	EIA bead method, cut off level of 4fg/ml.	Development of a kit that responds to a fully-automated system is needed.
A-15. Elastase 1	RIA Double antibody method	Determination method is 3 and a half hours (centrifugation necessary)	Time curtailed (1 step, beads), development of EIA
A-16. PGR	EIA beads	Determination time of approximately 20 hours, two washings.	Improvement of 1 step method

B. Items related to diabetes

Test items	Determination method	Current state	Problems, trends in development
B-1. Hemoglobin A1	Electrophoresis	Mainly column, all are manual methods	There has been no competition with AIC in terms of clinical significance or automation and therefore, there will be a trend toward reduction of the market.
B-2. Hemoglobin A1c	Column HPLC	Focusing on automation with columns	The market is slowly growing, but competition with fructosamine is a negative factor.
B-3. Urinary albumin	RIA, double antibody method RIA, solid phase method Immune turbidity Latex quantitative determination	The solid phase method has been used for RIA and therefore, there may be a change to a (DPC) simple solid phase method. Improved to a cut off level on the order of ug/ml with immune turbidity and latex.	Cost is the most important point with the development of immune turbidity. In the future the number of entry manufacturers is expected to increase.

Test items	Determination method	Current state	Problems, trends in development
B-4. anticipated Fructosamine	Colorimetry	Colorimetry (automation possible)	An increase in specimens is with automation.
B-5. 1.5-AG	Column	Determination time, 3 hours with manual method	Automation is a problem
C. Items related to liver disease			
C-1. Guanase	Colorimetry	Reagents for automation are on the market	Increase in specimens is proceeding with automation
C-2. ADA	UV method, rate	Automation is proceeding with UV-rate	An increase in specimens is proceeding
C-3. LCAT	Colorimetry	Endpoint colorimetry	Rate assay, automation assay, Development of new synthetic substrate (Daiichi Chemicals)
C-4 Hepatitis C virus	Enzyme antibody method	Enzyme antibody method, 40 to 50% positive rate with acute, chronic hepatitis-C	Kits for screening, improvement in positive rate
D. Items related to kidney disease			
D-1. NAG	Colorimetry	Automation possible (rate assay)	Increase in the number of specimens is expected to proceed with automation
D-2. AAP	Colorimetry	Manual end-point method	Automation and popularity of clinical significance
E. Others			
E-1. Immune complexes	EIA micro-plate	At the current time, self-adjusting reagents are often used	MBL is expected to be a new entry
E-2. Interferon	RIA (alpha, gamma) EIA (beta)	INF-alpha, gamma with RIA beads INF-beta with EIA solid phase method.	Establishment of clinical significance, NONRIA kit
E-3. Interleukin	EIA	EIA solid phase method, determination time of 5 hours	Establishment of clinical significance, curtailment of determination time.

2-3) Trends of infectious disease diagnostics

The market of infectious disease diagnostics is categorized into 6 sub-categories; bacteria test, immunological bacteria test, direct kit, virus antibody, virus antigen and immunological test. The outline of the whole market is described in Appendix 2-5) and an outline of each sub-category market is also given in Appendices 2-6) to 2-13).

Particularly the market for direct kits and virus tests (antibody and antigen) are gathering attention as follows:

1) Direct Kit

Test items are still limited and the market size is not large with annual sales of only 700 million yen. However, the market will be expanding because of such advantages as a short test period and the simplicity of the test. A-streptococcus is a major item. The market will expand further along with increasing number of test items, shortened test period (from 10 min to 3 min) and more use at small hospitals.

2) Virus Tests

Virus tests will continue to be important because they are greatly influential to blood transfusions, transovarial transmissions and STD's. The market is already sizable at 16 billion yen in 1989. Major test items are HBs, ATL (HTLV), AIDS (HIV) and HCV.

New test methods such as DNA probe will be introduced and the market will possibly be changing dramatically in 5-6 years.

Trends in each market are as follows:

Bacteria Test: Separation culture test, identification test and sensitivity test are major test items holding more than 85% of this market. Major products are biological culture media, simple identification kits and sensitivity discs which together hold approximately 80% of market share.

Immunological Bacteria Test: While the annual growth rate of identification kits by the immunological method is about 20%, that for the antiserum is only 1% because it is mainly used for type screening of infectious diseases. These trends will continue.

Direct Kit: The market is expected to expand along with the addition of new test items(now under development) such as mycobacterium tuberculosis, fungus, mycoplasma and campylobacter, the culturing of which is presently time-consuming.

Virus Antibody:	Expansion of the market is expected in ATLA and HIV, however the hospital market for HIV will not grow rapidly. The core market will continue to be in the area of blood transfusion and transovarial transmission. Typical test items are HB, ATL, rubella and toxoplasma.
Virus Antigen:	The main test item is now HB and market growth in such areas relating to STD as chlamydia and herpes is expected.
Immunological Test:	Syphilis and ASO are major test items and no rapid growth is expected.

The DNA probe market is still very small and now at a development stage as described in Appendix 2-14). Major market development plans by major companies are mentioned below:

Business name	In cooperation with	Products marketed	Future trends
Toray,	Life Technology (U.S.)	HPV screening	1) HPV kits will be used to check specimens that have been evaluated as false-negative in cell diagnoses. Consequently, they will become popular for screening.
Toray, Fuji-Bionics	Product import, clinical study facility	By the gross, 6, 11, 16, 18,31, 33 and 35 types are detected. Label is ^{32}P.	
	Juntendo University Dept. of Obstetrics and Gynecology Juntendo Urayasu Hospital		2) Potential markets will be regarded as 3,000,000 studies in combination with speciments of mass screening and diagnostics
	Chiba University Dept. of Obstetrics and Gynecology Chiba University 1st Dept. of Micro-biology		3) Since ^{32}P is used as the label the facilities used are limited to large study centres and university hospitals.
			4) The insurance score is estimated at 1,000 points.
	Eucaryotic Microbiology Research Center		5) Permission to import probes that can type individuals from gross detections will be applied for in the fall of 1989.
	Chiba Prefectural Anticancer Society		6) Studies are now being performed on changing from ^{32}P to ^{125}I as the label and on NONRIA substances.
			7) Of the diagnoses of infectious disease, non-A-non-B hepatitis virusis marketable and future trends include a demand for analysis and diagnosis of human genes.
Chugai Seiyaku	Gen-Probe(U.S.) Product import $2,700,000 paid for research and development (more than 378,000,000)	Tissue Culture Mycoplasma kit marketed for re-search in Decem-ber 1988. It is estimated that 5 products for mycoplasma,	1) The items that will be marketed in the future will all be marketed as in-vitro diagnostic drugs. Candidates for marketing in less than 2 to 3 years have already increased to 18 items.

Business name	In cooperation with	Products marketed	Future trends
	Research organization headed by Prof. Kawai of Jichi Medical University Respiratory system subcommittee STD subcommittee	Legionella TB, chlamydia, and gonococcus will be on the market in 1989. Characteristic of hybridization by liquid phase. Moreover, it is estimated that products for non-atypical acid-fast bacteria and mycobacteria will be on the market during the same period.	2) Of the many items on the market, TB is expected to show the most marketability. In addition, there is a trend toward marketing of items that can compete with conventional immunoassay. 3) Insurance scores are expected to be 300 to 500 points. 4) The photoluminescence detector for AE labeling is made by Gen-Probe Co. Import and selling of this and, in the future, developments of fully automated devices based on this device, are being considered.
Mitsubishi Yuka	Digene (U.S). Shares acquired Joint development with seller	It is estimated that 3 items of in situ kits will be introduced: 1) Cytomegalovirus 2) EB virus 3) HPV Labels are NONRIA and sensitivity is on the order of femto. Distribution of samples to research laboratories is expected.	1) There will finally be a trend from in situ kits toward being able to perform direct studies. This is a detection system with which only this sensitivity can be detected. 2) Companies with some contact with infectious decease and cancer will be the target. The field of HLA, risk factor and forensic medicine will not be among the targets. 3) Within two to 3 years it is expected that a group for DNA probe diagnosis will be formed at the research laboratory of Mitsubishi Yuka and that a research organization will also be produced.
Nichirei	School of Medicine Transplant Dept.	Registered in 1987 as the Hygiene Test Laboratory.	1)Methods will be revised to those that use PCR for typing by HLA southern blots, which

Business name	In cooperation with	Products marketed	Future trends
	Assistant Professor Hideo Inoko Professor Kimiyoshi Tsuji	Typing of HLA is being performed. But the market is small and was approximately 6,000,000 yen for 150 items in 1988. There is no tendency toward an increase and further expansion is doubtful.	are currently receiving 40,000 yen for 1 item, and do not employ probes with RFLP for evaluation by pattern recognition. The cost will thereby become 1/4. 2) Selling in Japan of mainly probes for infectious disease has also been attempted in the past by foreign venture businesses at Nichirei. As yet, studies have not been completed on rapid diagnosis and mother-child infections. These will be considered in the future after studies have been performed. These are regarded as in-vitro diagnostic drugs.
Toyo Boseki	Molecular Biosystems Dupont (U.S.) Import and selling of products	At the present time, the following probes are used as research reagents: 1. HBV 2. HSV 3. campylobacter 4. enterorirus 5. HIV 6. rotavirus 7. malaria Moreover, Taq polymerase related to PCR is also on the market.	1) The use of DNA probe diagnosis will emphasize confirmation diagnosis. HIV and ATL use definite diagnosis. Identification of pathogens of diarrhea may be employed for choice of antibiotics. 2) How to clinically use in-vitro diagnostic drugs will be in line with the policy of each company. Products that show superior specificity for an item will probably not be marketed as in-vitro diagnostic drugs.
Takara-shuzo	Orgenics Ltd., (Israel) "Chemiprobe" Product import Perkin-Elmer Co. Amplification device by PCR method	Import and selling of 16 items for cancer genes is being performed by Orgenics PCR amplification device has been	1) PCR is necessary in DNA probe diagnosis. Improvement of sensitivity is expected and this is expected to be the future basis for treatment in clinical laboratories. 2) Infectious diseases are the main target. However, conventional

Business name	In cooperation with	Products marketed	Future trends
		on the market from the fall of 1988 and 300 or more have been sold mainly to research laboratories.	methods have not been largely eroded. This is becoming a special type of study that is emphasized in study centres. 3) It is not as if actual items have already been targeted in terms of marketing of in-vitro diagnostic drugs and some are being marketed.
Eiken Kagaku	Company's own technology	Development is proceeding on a DNA probe diagnosis kit for typing of tuberculosis and marketing is anticipated. Type evaluation is performed after 2-3 weeks of cultivation. It is impossible to directly evaluate without cultivation with current sensitivity	1) The only significance is for tuberculosis on a commercial basis in terms DNA probe diagnosis. Even though there have been sales approaches from other companies, other items are being dismissed. 2) Optimum regions of amplification for each bacterium and virus must be researched in order to apply amplification by the PCR method and this is too costly.
Fuji Rebio	Tropix Co (U.S.) Seller of DNA probe diagnostic drugs Acquisition of shares	Diagnostic kits that use AMPPD labeling are under development by Tropix. Sensitivity is the same or better than that of isotope labeling.	1) Research will not be limited to use of AMPPD for only DNA probe diagnostics. 2) In order to increase popularity of DNA probes, development of an automated device is essential. Companies are competing in secret development. 3) Although HLA and ATL have been the targets for some period of time, they are not being opposed at the present time.
Fujisawa Pharmaceutical Co.	Onco (U.S.) Cosmo Bio. handles only probes	Sample distribution of DNA probe kits for HPV is anticipated (shortly).	1)Marketing as an in-vitro diagnostic drug is anticipated. There are plans for a type that carry screening a step further to group results into the 3 groups

Business name	In cooperation with	Products marketed	Future trends
		Labeling is by the colorimetric method NONRIA Use for screening whereby probes of 7 types: 6, 11, 16, 18, 31, 33, and 35 are evaluated by the gross.	of benign 6 and 11, malignant 16 and 18, and intermediate type 31 33 and 35 and evaluate types. 2) The eventual target is precision of centralized studies and diagnosis. This is significant because it will be possible to point out which individuals should be restudied by the evaluation type when there are many samples.
Wakunaga Seiyaku	Company's own technology	A method for detection of HPV using a double label primer was announced to the Japan Virology Association. Selling of HPV type 16 and TPV type 18 was started in June 1989 through Cosmo Bio.	1) The current goal is simply to sell probes. However, in the future, development of a system that has automated detectors will be emphasized. 2) It will probably be necessary to use a form that also includes extraction and amplification of DNA for this automation. The reaction in this case should probably be a liquid phase reaction.
Dainabot	Abbott (U.S.)	HBV-RI label kits are being sold for research. This ^{32}P label is changed to ^{125}I and it has been converted to column separation with liquid phase and is on the market in Japan. There has been an increase in RI facilities that use this product with conversion to ^{125}I. 12)	1) In addition to HB items, viral direct DNA diagnosis will be needed. ATL, HIV, EV, etc., will continue. However, it is concluded that DNA diagnosis is meaningless because only HSV is relatively easy to understand. 2) Amplification by PCR methods etc. is necessary for a system. However, since Dinabot does not appear to have a hand in the patent of Cetus, it can compete with reagent kits in terms of how detection is performed after amplification and therefore, development of a system is unnecessary.

Business name	In cooperation with	Products marketed	Future trends
			3) Basically, development and marketing of antiviral drugs will be pursued.

Business name	Current state	DNA as in-vitro diagnostic drug
Cosmo Bio	1) Handles probes of several companies as reagents for research and honors complete products of the industry. 2) Sales were 48,000,000 yen in 1989 and occupied 60% of the total market. 3) A programmable incubator that is employed with the PCR method has been recently used with good results by Fontbition-Bluegene (NONRIA detection system).	1)The conventional items of infectious disease can all be replaced with DNA probe diagnostics. 2) Marketing as an in-vitro diagnostic drug has already been considered. However, However, good products that are currently being handled will probably appear. 3) It appears that the patent on PCR of Cetus is the same patent that was completed earlier in Japan and therefore, it is not complete in its original form.
Wako Junyaku	1) Handles DNA probes of BRESA company as reagents for research. 2) The market is small with 1988 sales being 6,000,000.	1) Related associations, etc., are paying close attention to the Chugai Seiyaku and Toray probes and their operation. However, it does not appear that they can be used in test laboratories on their current level. 2) Pretreatment complexity, reproducibility, increasing speed, etc., are also problems. It appears that even though they actually work, these products still cannot be used when the fact that DNA sampling is difficult, back-ground data is necessary for bacteriology, etc., are taken into consideration. 3) However, emphasis is also being placed on how these products work on the clinical side when insurance scores have been assigned.

Business name	Current state	DNA as in-vitro diagnostic drug
Boehringer-Manheim Yamanouchi	A DNA-related kit for use as a reagent for research has been developed. NONRIA label "Digoxin" has recently been evaluated at a sensitivity of 0.1 pg.	1) There appears to be no market for this type of in-vitro diagnostic drug. At the current time, there are no prospects.
Amersham Japan	1) The current state is that DNA-related reagents for research are being sold and new products are being evaluated by studying chemical luminescence by exposing film using ECL genetic detection system and enzyme labeling, which were first sold in February 1989. 2) Actual probes that are handled are the infectious diseases.	1) At the current time, DNA probe diagnostics are not marketed as in-vitro diagnostic drugs. Amersham has been able to focus on expanded following of research laboratories and attention is being focused on new trends in DNA technology rather than on developments for use of DNA probes. 2) Consequently, in the future, new DNA fingerprint technology rather than kits for DNA probes will be emphasized in the future.
Dia-Iatron Iatron	1) The current state is that only the type of labeling and detection kit of photobitiu is being sold and it is rarely purchased. 2) This company is not paying any attention to differentiation biotin-avidin detection systems from older models.	1) Absorption of corresponding technology was also important with the boom in DNA probes in the past 3 to 4 years and research and development was performed by Mitsubishi Kasei. As a result, research was performed on the immature technological level, small market, etc., and a policy is established for eventual progress in this direction.

2-4) Trends in the market of other diagnostics: simple test, OTC, etc.

Simple tests in hospital include dry chemistry system, test paper for urinalysis, fetal occult blood, etc. OTC market includes pregnancy self-diagnosis and blood sugar self-diagnosis. In addition, the neonatal screening and mass screening markets are taken up here.

The current situation and future trends are as follows:

Subject item	Current situation and future trends
A. Simple Diagnosis	
1. Reagents for urine testing	The market in testing has increased slightly from the past. Nissui Pharmaceutical is a new entry since 1988. Boehringer-Mannheim Japan and Toho Yakuhin Kogyo merged in 1989, became Boehringer-Mannheim Toho and are marketing reagent strips. A new product is the test strips that detect urinary NAG produced by Miles-Sankyo.
2. Fecal occult blood	There are chemical methods represented by the guaiac method that detect human haemoglobin in the feces and methods that detect human haemoglobin. The former requires dietary restrictions because it also detects haemoglobin from fish, etc. Although the latter does not require dietary restrictions, it detects only haemorrhages from the large intestine and colon because human haemoglobin is broken down by the digestive juices. Consequently, it is effective in large intestine cancer screening. Its use has expanded rapidly in the past several years and predominates over chemical methods. The market-place will probably expand further if there is national support for mass screening.
3. Dry chemistry reagents and apparatus	Chemical test routine items are used in emergency testing in large and medium-sized hospitals, routine testing in small hospitals and doctors' private practice, bedside testing, etc., by manual apparatus (and some automatic) that easily and rapidly conduct testing. The reagents are films, test strips and tablets, and include those capable of measurement in whole blood and the types that measure plasma and serum. Although the conventional wet type simple analytical apparatus market predominates, there are presently more wet type reagent markets owing to the time lag that precedes substitution because of the cumulative large number of simple analytical apparatus. The most recent new entries include Backstar [phonetic], Konika, BMY and Kyoto Daiichi Kagaku. Development is also underway at Hoechst in Germany. Competition between companies will also flourish as the market expands.

Subject item	Current situation and future trends
4. Simple analytical apparatus and reagents	The functions and objectives indicate the wet type in the sameway as the aforementioned dry chemistry systems. Although the cumulative number of apparatus is large, as was mentioned above, a great many users are switching to the dry type and there is a marked tendency for the wet type to decrease.
5. HCG sample kits	These are products marketed by various companies since the second half of 1986. The difference from conventional products is that the measurement time is short at 2 to 3 minutes and they are extremely easy to use. There are two types of measurement methods, EIA and latex agglutination. Switching from conventional products to simple kits is already progressing. The HCG companies control the market and new entries, etc., are very difficult.
B. OTC	
1. Pregnancy self-diagnosis chemicals	Although these are products that have formed the market since 1986, there has been very strong resistance from groups such as the Japanese Society of Physicians, etc. from the start. The Ministry of Health and Welfare has also expressed disapproval. Agreement is current being reached through discussions between the manufacturers, specialists and Ministry of Health and Welfare. Nonetheless, as for recognition by the common user, advertising and publicity are limited and there has been no major market expansion. From the product standpoint, the measurement time is short (currently primarily within 30 minutes), the results can be checked from the day of the expected menstrual period (this could be done from 1 week after the expected menstrual period in the past), the existence of color changes is checked after examining the ring shapes, the q designation has been improved, etc. Several tens of companies have currently entered the market(some manufacturers have also already withdrawn). Competition between companies will probably become vigorous in the future.
2. Blood sugar self-measurement reagents and diabetes apparatus	These are small apparatus and reagents used for insulin-dependent diabetes patients to measure their own blood sugar values. There are said to be from 200,000 to 250,000 insulin-dependent in Japan. The cumulative number of such apparatus is from 70 to 80 thousand. Close to half of these are said to not be in use. This is because patients who are capable of monitoring themselves are limited and the apparatus are not used by the elderly, etc. Daikin Kogyo is expected to be a new entry. This company's product is said to be of the electrode type rather than the conventional test.

Subject item	Current situation and future trends
3. Pregnancy predicting drugs	Lion marketed Cephalon International's product in June 1987. However, there has been absolutely no business activity since that time. There are also currently no new entries and it is assumed that this market is not being formed.
4. Reagents for urine testing	The basic principle is the same as that of those used in hospital testing but the packaging units and test items are smaller. The major test items are glucose, pH and Protein. Sales center on diabetes patients. However, future market expansion is expected as common consumers become aware of health. Nonetheless, this is not mitigated because advertising and publicity are greatly restricted by the Drug Affairs Law, and market development is difficult.
C. Neonatal screening	This item is fixed as testing for congenital metabolic abnormality. This is purely a social burden. This screening is conducted primarily in the urban and rural prefectures and the government centers. However, the market is tending to decrease because the number of births is falling year by year. Among the current subjects, 17-OHP is an item that has been traced since January 1989 and must he conducted in 100% in 1989 in the preliminary stage in both urban and rural prefectures.
D. Mass screening	The mass screenings conducted in Japan are divided into periodic health examinations of workers, mass screening of students and those based on the Geriatric Health Preservation Law. The law concerning health examinations in workers was amended in 1989 and emphasis placed not only the early detection of diseases as in the past, but also on their prevention. Nonetheless, the examination rate is currently tending to drop and one can say that there is an urgent need to raise the examination rate. Student examinations are not thought to pose a particular problem. Heart examinations have been implemented in response to the increase in heart disease among younger persons in recent years. The examination rate is steadily increasing in the business of health maintenance of the elderly. Countermeasures that place emphasis on the health control of cancer, heart disease and stroke, which are said to he the three major adult diseases, are especially being strengthened.

The outline of diagnostics for circulatory organ disease is mentioned in Appendix 2-16. Major test items are CPK, CK-MB, total cholesterol, triglyceride, HDL cholesterol and Apo-lipo-proteins. The market trends of CPK, CK-MB and fat-related items such as total cholesterol are as follows:

A) CPK and CK-MB

CPK (CK) is a test item that has been established up to the present as a routine test. It is an item found in automatic chemical analyzers. Therefore, the automation rate is believed to be more than 95%.

There are UV and colorimetric (color) methods. However, the weight of the UV method is high. Although this is one of the minority test items for heart disease, CK- MB, which is an isozyme of CPK, has also been made into kits for the past several years.

CPK isozymes are fractionated into three types consisting of CK-BB, CK-MB and CK-MM. CK-MB is present in high concentrations in the myocardium. Therefore, there is a suspicion of heart disease such as myocardial infarction, etc. if CK-MB is elevated.

An examination of the current situation shows the number of CK-MB tests to be less than about 3% at approximately 1 million tests/year in comparison to the 35 million tests/year of the CPK test. Although it is not believed that a rapid increase can be expected even in the future, there is also a possibility of use as combination assay if new test items, etc. are developed.

B) Fat-related tests (total cholesterol and others)

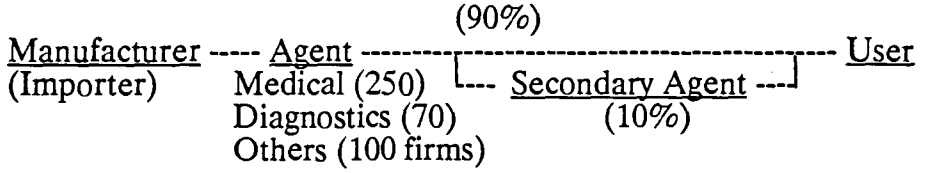
Total cholesterol, neutral fat and HDL cholesterol are ranked as representative tests among the various biochemical test items. The measurement methods emphasize enzyme methods. The automation rate is more than 95% and many of the products are highly perfected.

On the other hand, 6 types of apolipo-protein are known, apo A-I, A-II, B, C-II, C-III and apo E. Kits are available for the two types of measurement methods, SRID and immunoturbidimetry.

SRID reagents were marketed by Daiichi Kagaku Yakuhin in 1983. Immuno-turbidimetry reagents were made into kits in 1986. As a result, these are reagents found in automatic chemical analyzers.

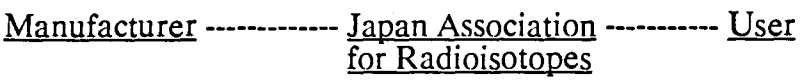
3. Characteristics of the Japanese Diagnostics Market

3-1) Distribution Channels



This is the sales channel common to each company. Normally, it is a route of flow from manufacturers to representative agents (through secondary agents in some cases) and then users. There are no direct sales when hospitals are the subjects.

A case where some sales are direct is the case of large commercial laboratories, etc. Moreover, the following channel, which is different from the aforementioned, is used for RIA (in-vitro) reagents:



The Japan Association for Radioisotopes is the only representative and is the aforementioned flow for all RIA reagents. However, flow of substances is from manufacturer directly to user and there are cases where the association handles some of the substances. Consequently, in almost all cases, the same association gives a note of receipt as a voucher and is in charge of money.

3-2) Presence of Agents

The following reasons can be given for the existence of representatives between manufacturers and users.

A) Users usually prefer to have one contact for each category, i.e. drugs, diagnostics and medical equipment, in order to avoid complexities in the handling of business transactions. All preparations necessary in hospitals and commercial laboratories cannot be done by the manufacturer, and therefore, special representative functions are necessary.

Representative branches can respond to the needs of users by corresponding with other branches without directly talking with the manufacturer.

B) On the manufacturer's side, the appropriate number of businessmen, marketing points, stock points, etc., are needed in order to directly deal with 6,000 to 7,000 users nationwide.

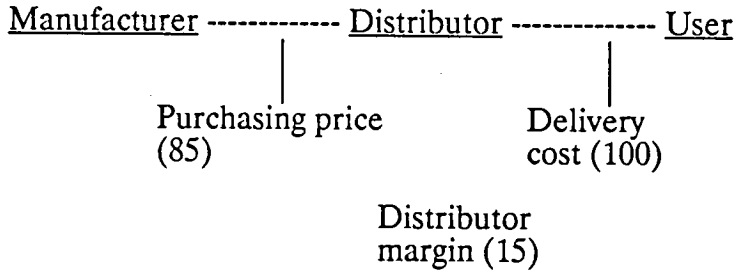
This puts a considerable economic burden on each company, regardless of their business scale. The use of businessmen as agents is very advantageous to the manufacturer. The use of agents has been discussed from the user's point of view and the manufacturer's point of view. The main role and functions of the agents are shown below.

3-3) Role, functions of agents: receives orders for commercial products, delivery business, payment recovery.

Drug information activities are rarely performed. Moreover, hard maintenance of devices, etc., is rarely performed. (Maintenance supervisors are sometimes stationed in large branches.) Therefore, the manufacturer is usually in charge of drug information activities and maintenance.

3-4) Distributor Margin

The margin of the distributor varies with the case, but it is usually in the following form:



However, there are many cases where a delivery cost of 100 to the user is not list price and is generally 20 to 40% with some type of reduction. Consequently, the user delivery cost is 20% of the list price in the case of 20% in the aforementioned example and if list price is 100, it is delivery for 80. Fifteen branches get 15% of the delivery price of 80 and therefore, it is 12 to a list price of 100. The price given to branches by the manufacturer is the delivery cost 80 - 12 (branch margin) = 68 (manufacturers shipping cost). The manufacturer gives the branch as much as 68% of the list price. The aforementioned is generally true in the case of hospitals. However, the reduction rate to commercial laboratories (particularly large laboratories) is as much 40% of the list price and depending on the case, can be 50% or more.

Many cases involve manufacturer-direct sales because there are no representative branches.

Moreover, there are also cases where the method is adopted whereby the margin rate is dropped somewhat and 2% to 3% of the total semi-annual or annual sales (target predetermined by manufacturer and representative office) is kicked back.

There are many manufacturers that periodically use the kick back system as payments during new product campaigns, etc.

In addition, it should be noted that the representative branch is not a representative of one specific manufacturer. The branch office performs the business of several manufacturers. Therefore, importance is placed on products with a high margin rate and on commercial products with great demand. The products of several manufacturers are used because the needs of users cannot be met with the products of just one company and transactions are not possible.

In any case, branch offices are important to the manufacturer because they provide sufficient contact with hospitals. It is necessary to recognize and use the features and functions of these agents.

3-5) Correspondence with Hospitals (Commercial Laboratories)

This is a field supervised by the manufacturer (the responsible person in charge of drug information. The user is educated and publicity is given on the commercial products and new products of the company and these activities are performed from use to price negotiations.

There are several negotiating windows on the hospital side, but the areas that directly participate in use are as follow:

A) Test head: This is the key person controlling use of products and high-ranking supervisors of the test area. However, there are many cases where authority for consumer goods that are used every day, such as diagnostics, etc., is transferred to technical heads who are plant supervisors.

B) Technical heads: Site supervisors who generalize technology. These are key persons who pay the most attention to the manufacturer and perform actual tests of use of diagnostics, etc.

C) Chief technicians: Supervisors of each area (biochemistry haematology, etc.). They represents areas of the use of diagnostics, etc., and report to the technical heads. They must have sufficient contact with the DI person.

D) Supplies and Purchasing: This section is responsible for purchasing products used by hospitals, etc. It is also in charge of diagnostics. There is a particularly strong need for prices, etc. and therefore, there must be sufficient correspondence with the manufacturer. Supplies and purchasing should receive attention in addition to the contact with the test areas.
There are also cases where this area is more important than test areas, depending on the hospital.

E) Commercial Laboratories: There are sections that are in charge of purchasing in commercial laboratories and these sections are a contact point. It is necessary to follow test supervisors and area supervisors (equivalent to main technicians in hospitals) because evaluation of products and service, etc., correspondence with the plant side are important.

Furthermore, there is a marked reduction in cost because large amounts are purchased when compared to hospitals, as previously mentioned. Consequently, each company's prices for hospitals and prices for commercial laboratories should be differentiated.

Since there are important clients who consider the cost high even with a cost reduction, each company sets its own priority DI persons.

The aforementioned has been a general summary of the market structure in Japan, industrial business, commercial practice, correspondence between the representative branch offices and users,etc. In conclusion, the following points should be given consideration:

Many Japanese industries are aware of the aforementioned and have reached the aforementioned points in terms of technology also. Don't take it so easy. Consequently, there have been mistakes with incomplete participant methods during sales promotion.

What is called the medical industry pertains to many types of industries and users that have been connected for many years. Even up to the private side, business seem complicated. For instance, to become successful, doctors who come up to Tokyo must also take into consideration life styles and diet. There can also be a connection with golf. Of course, this type of correspondence is not always necessary, but is often the case. Use of commercial products is also controlled by normal foundations. Large economic outlays are needed for businesses to market their products.

When new products come to the market, they first must receive approval for manufacture and import before being sold. However, where this will first be attempted is of considerable importance. In Japan, there are several medical associations made up of specialists. Doctors therefore play a central role. There is a so-called "don(boss)". There are doctors that are followers of these central doctors, they have juniors. A hierarchy is thereby formed. These doctors have considerable influence, and this influence forms contacts that is spread horizontally throughout the country.

To return to the original topic, it is useless to market new products unless one starts with this "don".

It is necessary to recognize the top of each field in order to be successful in this industry.

4. Outline of 30 Major Diagnostic Producers

4-1) Company outline

Company Name	Address & Phone No.	Established	Capital (mil. yen)	Employ.	Sales (mil. yen)
Amersham Japan	5-1-3 Hakusan, Bunkyo-ku, Tokyo 03-816-6450	Apr. '82	250	45	3,400
Boehringer-M-Yamanouchi	3-10-11 Toranomon, Minato-ku, Tokyo 03-432-3151	Jan. '73	80	220	7,900
Chugai Pharmaceutical	2-1-9 Kyobashi, Chuo-ku, Tokyo 03-281-6611	Mar. '43	19,193	3,588	124,492
Daiichi Pure Chemical	3-13-5 Nihonbashi, Chuo-ku, Tokyo 03-272-0671	Jul. '47	960	770	18,426
Daiichi Radioisotope	3-10-5 Nihonbashi, Chuo-ku, Tokyo 03-272-1625	Dec. '68	400	370	12,200
Dainabot	3-8-21 Toranomon, Minato-ku, Tokyo 03-437-9441	Aug. '77	935	780	30,600
Denka Seiken	12-1 Nihonbashi-Kabutocho, Chuo-ku, Tokyo 03-669-9091	Feb. '50	101	319	3,408
Eiken Chemical	1-33-8 Hongo, Bunkyo-ku, Tokyo 03-813-5401	Feb. '39	2,002	770	16,172
Eisai	4-6-10 Koishikawa, Bunkyo-ku, Tokyo 03-817-3700	Dec. '41	19,354	3,803	186,411
Fuji Rebio	2-7-1 Nishi-Shinjuku, Shinjuku-ku, Tokyo 03-348-0691	Dec. '50	3,683	752	19,635
Fujisawa Pharmaceutical	3-4-7 Doshomachi, Chuo-ku, Osaka 06-202-1141	Dec. '30	16,281	5,454	208,643
Hoechst Japan	8-10-16 Akasaka, Minato-ku, Tokyo 03-479-5111	Dec. '66	1,580	1,735	85,000
Iatron	2-1-11 Higashi-Kanda, Chiyoda-ku, Tokyo 03-862-1761	Jun. '60	80	239	6,388
International Reagents	2-1-30 Hamabedori, Chuo-ku, Kobe 078-231-4151	Dec. '69	2,650	314	10,473
Japan Becton-Dickinson	8-5-4 Akasaka, Minato-ku, Tokyo 03-403-9991	May '85	750	200	6,000
Kainos Laboratories	4-2-1 Yushima, Bunkyo-ku, Tokyo 03-816-4123	May '75	98	131	3,650
Kyokuto Pharmaceutical	3-1-1 Nihonbashi-Honcho, Chuo-ku, Tokyo 03-270-8629	Jul. '52	36	200	4,600
Kyowa Medex	1-6-1 Otemachi, Chiyoda-ku, Tokyo 03-282-0092	Apr. '81	250	200	4,963
Miles-Sankyo	1-9-7 Ginza, Chuo-ku, Tokyo 03-567-5511	Feb. '67	250	303	9,203
Mochida Pharmaceutical	1-7 Yotsuya, Shinjuku-ku, Tokyo 03-358-7211	Apr. '45	4,365	1,896	49,791
Nippon Roche	3-2-3 Marunouchi, Chiyoda-ku, Tokyo 03-214-5371	May '32	13,200	1,607	49,300
Nissui Pharmaceutical	2-11-1 Sugamo, Toshima-ku, Tokyo 03-918-8161	Apr. '35	880	380	10,366
Ono Pharmaceutical	2-1-5 Doshomachi, Chuo-ku, Osaka 06-222-5551	Jul. '47	17,336	1,676	73,000
Sanko Junyaku	1-10-6 Iwamoto-cho, Chiyoda-ku, Tokyo 03-863-3261	May '54	1,173	238	6,017
Sankyo	2-7-12 Ginza, Chuo-ku, Tokyo 03-562-0411	Mar. '13	27,883	5,979	308,510
Shino-Test	10 Ichibancho, Chiyoda-ku, Tokyo 03-239-3741	Mar. '53	140	259	5,369
Shionogi	3-1-8 Doshomachi, Chuo-ku, Osaka 06-202-2161	Jun. '19	21,117	6,467	216,077
Toray-Fuji Bionics	1-11-12 Kitamachi, Nerima-ku, Tokyo 03-937-0531	Nov. '82	450	40	3,320
Yamanouchi Pharmaceutical	2-3-11 Nihonbashi-Honcho, Chuo-ku, Tokyo 03-244-3200	Mar. '39	24,700	3,220	164,053
Wako Pure Chemical	3-1-2 Doshomachi, Chuo-ku, Osaka 06-203-3741	Jun. '22	2,060	1,128	42,337

4-2) Sales Results of Diagnostics by 30 Major Companies

(Million Yen)

Company Name	1985	1986	1987	1988	1989
Amersham Japan	1,265	1,434	1,740	1,900	2,000
Boehringer-M-Y	3,520	4,257	4,400	4,800	5,100
Chugai Pharmaceutical	2,500	2,400	2,390	2,310	2,200
Daiichi Pure Chemical	5,100	5,200	5,750	6,100	6,860
Daiichi Radioisotope	6,700	7,000	7,370	7,560	7,930
Dainabot	14,200	16,300	16,400	15,850	16,500
Denka Seiken	1,512	1,628	1,729	1,882	1,950
Eiken Chemical	11,589	12,243	12,800	4,950*1	13,532
Eisai	1,080	1,170	1,290	1,380	1,600
Fuji Rebio	6,134	7,500	10,013	11,350	12,600
Fujisawa Pharmaceu.	1,490	1,194	937	790	820
Hoechst Japan	4,080	4,450	5,300	6,100	6,300
Iatron	3,280	3,600	3,900	4,350	4,500
International Reagents	7,268	7,920	8,815	9,698	9,225
Japan Becton-Dickinson	1,400	1,500	1,750	1,950	2,050
Kainos Laboratories	2,400	2,540	3,000	3,250	3,500
Kyokuto Pharmaceu.	2,279	2,678	2,987	3,209	3,710
Kyowa Medex	4,185	4,375	4,181	4,163	4,300
Miles-Sankyo	7,380	8,000	8,270	7,950	8,000
Mochida Pharmaceu.	4,203	4,305	4,360	3,210	3,060
Nippon Roche	1,800	1,995	2,290	2,635	2,750
Nissui Pharmaceutical	5,300	5,700	6,000	6,300	6,450
Ono Pharmaceutical	5,850	6,020	6,307	6,256	6,400
Sanko Junyaku	6,082	6,822	6,290	4,122	3,950
Sankyo	5,440	5,580	5,680	6,140	6,780
Shino-Test	3,801	4,710	4,763	4,829	4,950
Shionogi	3,747	3,788	4,150	4,400	4,900
Toray-Fuji Bionics	880	1,830	2,270	3,300	3,600
Yamanouchi Pharmaceu.	1,220	1,310	1,380	1,450	320*2
Wako Pure Chemical	9,555	9,850	10,140	10,230	10,350

Note: *1) 5 months sales value from Nov.'87 to Mar.'88
*2) 3 months sales value from Jan.'89 to Mar.'89

4-3) Sales by Test Field

(Million Yen)

Test Field / Company Name	General	Haemato.	Biochem	Immunosero.	RIA	Microbio.	Control	Pathology
Amersham Japan	-	-	-	-	2,000	-	-	-
Boehringer-M-Y	-	550	3,350	1,200	-	-	-	-
Chugai Pharmaceutical	-	-	2,000	200	-	-	-	-
Daiichi Pure Chemical	70	750	4,400	1,200	-	190	250	-
Daiichi Radioisotope	-	-	-	-	7,930	-	-	-
Dainabot	-	-	1,650	4,000	10,200	-	-	0
Denka Seiken	-	-	1,100	750	-	100	-	-
Eiken Chemical	1,490	202	3,385	3,830	1,380	3,245	0	-
Eisai	-	720	-	880	-	-	-	-
Fuji Rebio	-	-	350	11,000	-	0	-	-
Fujisawa Pharmaceu.	60	150	0	420	-	60	-	130
Hoechst Japan	300	450	300	4,500	550	-	-	-
Iatron	-	100	3,450	850	-	0	100	-
International Reagent	-	1,700	3,900	2,218	-	-	1,880	0
Japan Becton-Dickinson	-	-	-	455	-	1,585	-	-
Kainos Laboratories	-	-	2,050	1,050	-	-	400	-
Kyokuto Pharmaceu.	-	-	1,850	400	-	1,450	10	-
Kyowa Medex	-	-	3,910	390	-	-	-	-
Miles-Sankyo	4,650	60	2,430	220	-	70	70	450
Mochida Pharmaceu.	-	-	-	3,060	-	-	-	-
Nippon Roche	-	90	220	650	525	1,150	-	-
Nissui Pharmaceutical	0	-	1,050	1,500	-	3,500	400	-
Ono Pharmaceutical	2,870	400	2,180	550	-	-	150	250
Sanko Junyaku	-	50	2,050	1,200	-	500	150	-
Sankyo	3,150	885	1,210	830	-	0	240	465
Shino-Test	-	160	3,500	700	-	20	570	0
Shionogi	1,250	-	600	500	2,550	-	-	-
Toray-Fuji Bionics	-	-	-	-	3,300	-	-	-
Yamanouchi Pharmaceu.	230	-	50	50	-	-	-	-
Wako Pure Chemical	120	145	9,630	350	-	0	105	0

4-4) Case Study for Major Diagnostic Producers

DAINABOT CO., LTD.

1. Company Outline

Mail Address: 3-8-21 Toranomon, Minato-ku, Tokyo 105
Phone: 03-437-9441
Fax: 03-437-9367
Telex: J26369
Established: August 1977
Representative: J. B. Johnston
Capitalization: Yen 935 million
Employees: 780
Major Shareholders: Abbott Laboratories, Daiichi Seiyaku
Financial Results (Million Yen):

	Nov. 87	Nov. 88	Nov. 89
Sales	30,100	30,600	32,000
Profit	-	-	-

2. Sales of Diagnostic Division (Million Yen):

	Nov. 85	Nov. 86	Nov. 87	Nov. 88	Nov. 89
Diagnostic reagents	14,200	16,300	16,400	15,850	16,500
Test equipment	1,300	1,400	1,500	1,600	1,700
Others	2,100	2,200	2,300	2,400	2,450
Total	17,600	19,900	20,200	19,850	20,650

Note: Sales of test equipment include automatic chemical analyzer, simple analyzer (VISION) and equipment for bacteria tests. Since TDX and IMAX are in most cases for rent, the sales of these systems are very small. Others include RIA (in-vivo).

3. Sales of Diagnostics by Area (Million Yen):

Test Area	Nov. 85	Nov. 86	Nov. 87	Nov. 88	Nov. 89
General	-	-	-	-	-
Haematological	-	-	-	-	-
Biochemical	1,500	1,550	1,600	1,650	1,750
Immunoserological	2,200	4,350	4,500	4,000	4,650
Microbiological	-	-	-	-	-
Control	-	-	-	-	-
RIA	10,500	10,400	10,300	10,200	10,000
Total	14,200	16,300	16,400	15,850	16,500

4. Rank and Characteristics in the Diagnostics Market

This company is a merger formed by the world's largest diagnostics manufacturer Abbott Co. of the United States and Dainippon Seiyaku. Its major business is the sale of pharmaceuticals and diagnostics.

It is ranked as the top manufacturer in Japan as well and leads the industry especially in the fields of RIA (in-vitro), EIA and FIA.

Currently emphasized products include IMX (immunoautomation apparatus), test packs (EIA simple diagnostic kits) and VISION (simple diagnostic system for biochemistry), etc.

5. Actual Sales of Top Five Products

unit (million yen)

rank	product	December 1989 (estimated)
1	general test reagents	4,650
2	Glucostix	2,000
3	Glucostar (apparatus)	330
4	Seralyzer reagents	200
5	Seralyzer (apparatus)	130

6. Conditions of Cooperation

1) Capital

Merger of Abbott Co. of the United States and Dainippon Seiyaku.

2) Sales

Sale of the biochemical simple analysis systems VISION and Test pack (HCG, strip A) were consigned to Shionogi Seiyaku in 1987. However, these are joint sales with Dainabot. Sales are weak in medium sized and small hospitals and private practitioners. Dainabot's cooperation is intended to intensify the sales power.

7. Development Trends

Although RIA is made by the company itself (some products are imported), the other products are imported from Abbott Co.

The major domestic activity is marketing activity in the existing market. There is also information gathering and publicity activity such as predicting the market for new products, investigating needs, etc.

EIKEN CHEMICAL CO., LTD.

1. Company Outline

Mail Address: 1-33-8 Hongo, Bunkyo-ku, Tokyo 113
Phone: 03-813-5401
Fax: 03-818-1207
Representative: Tadao Kurozumu, President
Capitalization: Yen 2,002 million
Employees: 770
Major shareholders: Tanabe Seiyaku (50.3%), T. Kurozumi (5.2%), etc.
Financial Results (Million Yen):

	Oct. 87	Mar. 88 (5 months)	Mar. 89
Sales	14,305	5,807	16,172
Profit	348	101	300

2. Sales of Diagnostic Division (Million Yen):

	Oct. 85	Oct. 86	Oct. 87	Mar. 88	Mar. 89
Diagnostic reagents	11,589	12,243	12,800	4,950	13,532
Test equipment	20	30	50	50	140
Others	199	230	1,455	807	2,500
Total	11,808	12,503	14,305	5,807	16,172

Note: Settlement term was changed to March from 1988.
Test equipment includes LA system and blood glucose self-monitoring system. Others include contract testing business until Oct. 86 and sales of contrast media additionally from Oct. 87.

3. Sales of Diagnostics by Area (Million Yen):

Test Area	Nov. 85	Nov. 86	Nov. 87	Nov. 88	Nov. 89
General	1,200	1,300	1,400	545	1,490
Haematological	160	180	200	75	202
Biochemical	2,960	3,050	3,140	1,240	3,385
Immunoserological	3,079	3,403	3,640	1,400	3,830
Microbiological	2,890	3,000	3,100	1,190	3,245
Control	0	0	0	0	0
RIA	1,300	1,310	1,320	500	1,380
Total	11,589	12,243	12,800	4,950	13,532

Remarks:

1) Eiken is third largest producer of general diagnostics after Miles-Sankyo and Boehringer-Manheim-Yamanouchi. Recently efforts are put on diagnostics for OTC.
2) Blood glucose self-testing diagnostic is most active in the biochemical area.
3) LA system, "Strep-A" and feces occult blood are major products in the immuno- serological area. DNA probe diagnostic for identifying type of tuberculosis is currently under development.
4) NSE and urine albumin are major products in the RIA area.

4. Rank and Characteristics in the Diagnostics Market

This is the next largest domestic manufacturer to Dainabot. Eiken also entered the contrast media market in 1987 and plans to enlarge its business scale. Preparations are said to be underway.

The company basically started as a manufacturer of media for bacterial testing. It currently has products in almost all clinical test fields and has undergone broad development.

The capital system is the Tanabe Seiyaku system. Sales channels that centered on the drug wholesalers of the same company were established and it is also a domestic manufacturer distinguished in both technical and sales power.

5. Actual Sales of Top Five Products

unit (million yen)

rank	product	March 1989 (estimated)
1	bacterial testing, raw media	1,000
2	LA reagents	990
3	C R P	900
4	simple identification	880
5	A S O	870

Others include sensitivity disks (650 million yen), powdered media (450 million yen), Pregnancy diagnostics (350 million yen), etc.

6. Conditions of Cooperation

1) Capital cooperation
Investment by Tanabe Seiyaku (50.3%)

Alpha-Tech equipment sales and Eiken materials sample container production as a 100% subsidiary.

2) Sales cooperation

Tanabe Seiyaku's sales channels (total sales source) and DI (drug information) activity by Eiken itself.

3) Technical cooperation

X-ray contrast media production technology of Guerbet S. A. of France introduced.

Licensing agreement with Mitsubishi Kasei concerning immune diagnosis apparatus and reagents.

7. Development Trends

In relation to the LA system, a large full automatic model LX3OOO was marketed in 1989 and items associated with TDM and viruses are being developed.

Attention is turned to direct kits by bacteria-associated immunologic methods, diagnostics for OTC, DNA probe diagnosis (for evaluating the type of tubercle bacillus), etc.

FUJIREBIO INC.

1. Company Outline

Mail Address: 2-7-1 Nishi-Shinjuku, Shinjuku-ku, Tokyo 163
Phone: 03-348-0691
Fax: 03-342-6220
Established: December 1950
Representative: Masaru Fukuyama, President
Capitalization: Yen 3,683 million
Employees: 752
Major Shareholders: Ajinomoto (9.3%), Nippon Life Insurance (6.3%), Toray Industries (6.1%), Yamanouchi Pharmaceutical (4.9%)
Financial Results (Million Yen):

	Dec. 87	Dec. 88	Dec. 89 (est)
Sales	17,070	19,635	21,000
Profit	902	1,052	1,100

2. Sales of Diagnostic Division (Million Yen):

	Dec. 85	Dec. 86	Dec. 87	Dec. 88	Dec. 89 (est)
Diagnostic reagents	6,134	7,500	10,013	11,350	12,600
Test equipment	260	300	400	450	450
Others	-	-	-	-	-
Total	6,394	7,800	10,413	11,800	13,050

Note: The sales of diagnostics are continuing to grow steadily. Immunoserological products share 95% of the sales and ATL and CA19-9 in particular contribute to the increase of sales.
Major products in the test equipment area are diluter and EIA system. Sales are stable.

3. Sales of Diagnostics by Area (Million Yen):

Test Area	Dec. 85	Dec. 86	Dec. 87	Dec. 88	Dec. 89 (est)
General	-	-	-	-	-
Haematological	-	-	-	-	-
Biochemical	290	300	350	350	400
Immunoserological	5,844	7,200	9,663	11,000	12,200
Microbiological	0	0	0	0	0
Control	-	-	-	-	-
RIA	-	-	-	-	-
Total	6,134	7,500	10,013	11,350	12,600

4. Rank and Characteristics in Diagnostics Market

This is an enterprise that started from a blood bank and entered the diagnostics field in 1965. It is the number 3 domestic manufacturer following Dainabot and Eiken Chemical. Its development effort has received particular acknowledgment. It also has strong ties with the Japan Red Cross because of its start as a blood blank. The most recent example is an HIV-III diagnostic. Although screening tests were begun (by the Japan Red Cross) using a Dainabot product (ELISA) in October 1986, there was a 100% conversion to the Fuji Rebio product 1 year later (PA method).

The company has SRL which is the largest domestic commercial laboratory as a subsidiary.

5. Actual Sales of Top Five Products

unit (million yen)

rank	product	December 1989 (estimated)
1	syphilis (TPHA)	2,800
2	HIV-III (PA)	1,680
3	ATL (PA)	1,600
4	HBS antigen (RPHA)	1,560
5	HBS antibody (PHA)	1,280

In addition, CA19-9 (EIA) is 780 million yen. The characteristic of this company is that the sales of individual products are extremely large. The recently marketed HIV- III, ATL, CAl9-9, etc., are all becoming hit products.

6. Conditions of Cooperation

1) Capital

Ajinomoto, Toray, Yamanouchi Seiyaku, etc., all have capital participation.

2) Sales

Bulk supplies of CAl9-9 and CA125 antisera are received from Centocor, Inc. of the United States.

3) Technology

There is cooperation on the technology introduction and sales rights of DNA diagnostics by AMPPD labelling from the Tropic Co. of the United States.

7. Development Trends

Development of HBV and ATL by DNA probe methods.

Production of reagents for type C hepatitis virus testing by PA (requested from Ortho Diagnostic Systems).

Development of Ig ERAST test reagents in relation to allergy (EIA).

WAKO PURE CHEMICAL INDUSTRIES, LTD.

1. Company Outline

Mail Address: 3-1-2 Doshomachi, Chuo-ku, Osaka 541
Phone: 06-203-3741
Fax: 06-201-5964
Established: June 1922
Representative: Rokuro Takeda, President
Capitalization: Yen 1,060 million
Employees: 1,128
Major Shareholders: Takeda Chemical (68.1%), Fuji Photo Film (9.6%)
Financial Results (Million Yen):

	Mar. 87	Mar.88	Mar.89
Sales	36,419	39,477	42,337
Profit	2,774	3,101	3,887

2. Sales of Diagnostic Division (Million Yen):

	Mar. 85	Mar. 86	Mar. 87	Mar. 88	Mar. 89
Diagnostic reagents	9,555	9,850	10,140	10,230	10,350
Test equipment	45	50	60	70	85
Others	-	-	-	-	-
Total	9,600	9,900	10,200	10,300	10,435

3. Sales of Diagnostics by Area (Million Yen):

Test Area	Mar. 85	Mar. 86	Mar. 87	Mar. 88	Mar. 89
General	90	100	110	120	120
Haematological	100	110	120	130	145
Biochemical	9,065	9,300	9,530	9,575	9,630
Immunoserological	225	255	290	310	350
Microbiological	0	0	0	0	0
Control	80	85	90	95	105
RIA	-	-	-	-	-
Total	9,555	9,850	10,140	10,230	10,350

Remarks: More than 90% of the diagnostic sales are concentrated in the biochemical area and the expansion of business to other areas will be required.

4. Rank and Characteristics in Diagnostics Market

This is an enterprise formed of three pillars, pharmaceutical intermediates, industrial reagents and clinical test reagents. The diagnostics are reagents for biochemical testing and this is the manufacturer with the best actual results. However, the considerable lag in other fields is conspicuous.

Attempts to move into the immune sera fields such as EIA, etc., have recently been strengthened. Nonetheless, the walls raised by other preceding companies are thick and there will be a considerable battle without giving the desired results.

5. Actual Sales of Top Five Products

unit (million yen)

rank	product	March 1989 (estimated)
1	total cholesterol	920
2	neutral lipid	660
3	//beta// lipoprotein	580
4	free fatty acid	490
5	amylasen	450

6. Conditions of Cooperation

1) Capital

68.1% capital from Takeda Yakuhin Kogyo and 9.6% from Fuji Film.

2) Sales

Sanyo Kasei: sale of EIA reagents.

Olympus Kogaku: sale of this company's immune automatic system PK3OO series.

7. Development Trends

Development of EIA reagents (cancer markers, hormones, items associated with infectious disease). Enlargement of immunoturbidimetry test items.

INTERNATIONAL REAGENTS CORPORATION

1. Company Outline

Mail Address: 2-1-30 Hamabedori, Chuo-ku, Kobe 651
Phone: 078-231-4151
Fax: 078-232-0548
Established: December 1969
Capitalization: Yen 2,650 million
Employees: 314
Major Shareholders: Green Cross (63.0%), etc.
Financial Results (Million Yen):

	Dec. 87	Dec. 88	Dec.89 (est)
Sales	9,522	10,473	10,000
Profit	1,008	1,109	1,000

2. Sales of Diagnostic Division (Million Yen):

	Dec. 85	Dec. 86	Dec. 87	Dec. 88	Dec. 89 (est)
Diagnostic reagents	7,268	7,920	8,815	9,698	9,225
Test equipment	476	528	546	600	600
Others	173	164	161	175	175
Total	7,917	8,662	9,522	10,473	10,000

Note: Test equipment includes EIA reader, blood coagulation system, etc. Others include reagents for research and development. 1989 sales are expected to decrease, most likely due to the effect of IRC's parent company's (Green Cross) violation of the pharmaceutical affairs law.

3. Sales of Diagnostics by Area (Million Yen):

Test Area	Dec. 85	Dec. 86	Dec. 87	Dec. 88	Dec. 89 (est)
General	-	-	-	-	-
Haematological	1,300	1,450	1,565	1,700	1,600
Biochemical	2,868	3,100	3,500	3,900	3,750
Immunoserological	1,500	1,700	2,000	2,218	2,075
Microbiological	-	-	-	-	-
Control	1,600	1,670	1,750	1,880	1,800
RIA	-	-	-	-	-
Total	7,268	7,920	8,815	9,698	9,225

4. Rank and Characteristics in the diagnostics Market

This company was started in 1969 as a merger of Green Cross and the American Hospital Supply Corporation of the United States (currently Baxter). Import sales of the Dado products (test reagents associated with blood transfusions, etc.) were begun.

Thereafter, as the company constructed its own plants, it grew into a top level enterprise by producing reagents for biochemical testing and expanding successive manufacturing tasks.

The current emphasis is on biochemical testing with expansion into the fields of immunology and haematology.

5. Actual Sales of Top Five Products

unit (million yen)

rank	product	December 1989 (estimated)
1	control sera	1,400
2	neutral lipid	560
3	control corpuscle plasma	400
4	Coombs	400
5	fibrinogen	380

6. Conditions of Cooperation

1) Capital

63% capital from Green Cross.

2) Sales

Import sales of Dado antisera for blood type evaluation, control, biochemical test reagents, etc.

Sale of Japan Green Cross HB related reagents.

Import sales of ENI Inc. HIV antibody kit (EIA).

Sale of blood coagulation apparatus (produced by Kyoto Daiichi Kagaku).

7. Development Trends

Attention is turned to the immune sera test field.

It is entering the EIA field by marketing the "Elsia-Auto", an automatic apparatus for the EIA heteromicroplate method.

MILES-SANKYO CO., LTD.

1. Company Outline

Mail Address: 1-9-7 Ginza, Chuo-ku, Tokyo 104
Phone: 03-567-5511
Fax: 03-561-6673
Established: February 1967
Representative: D. R. Hoffman, President
Capitalization: Yen 250 million
Employees: 303
Major Shareholders: Sankyo (45%), Miles Inc. (45%), Ono Pharmaceutical (10%)
Financial Results (Million Yen):

	Dec. 87	Dec. 88	Dec. 89 (est)
Sales	9,600	9,203	9,300
Profit	984	898	900

2. Sales of Diagnostic Division (Million Yen):

	Dec. 85	Dec. 86	Dec. 87	Dec. 88	Dec. 89 (est)
Diagnostic reagents	7,380	8,000	8,270	7,950	8,000
Test equipment	910	1,000	1,100	1,000	1,000
Others	-	-	-	-	-
Total	8,290	9,000	9,370	8,950	9,000

3. Sales of Diagnostics by Area (Million Yen):

Test Area	Dec. 85	Dec. 86	Dec. 87	Dec. 88	Dec. 89 (est)
General	4,360	4,720	4,840	4,650	4,650
Haematological	45	50	60	60	70
Biochemical	2,310	2,500	2,600	2,430	2,450
Immunoserological	150	180	200	220	240
Microbiological	55	60	70	70	70
Control	60	70	80	70	70
Pathology	400	420	430	450	450
Total	7,380	8,000	8,270	7,950	8,000

4. Rank and Characteristics in the Diagnostics Market

This company was founded in 1967 as Japan Ames by joint investment by Miles Laboratories of the United States, a subsidiary of the West German any Bayer Co., Sankyo and Ono Yakuhin. The name was changed to the present name in 1970 and it is the top domestic manufacturer of urinalysis test reagents, blood sugar self-measurement reagents, etc. Sales are entrusted to both Sankyo and Ono Yakuhin.

5. Actual Sales of Top Five Products

unit (million yen)

rank	product	December 1989 (estimated)
1	general test reagents	4,650
2	Glucostix	2,000
3	Glucostar (apparatus)	330
4	Seralyzer reagents	200
5	Seralyzer (apparatus)	130

Gluco-stick are a blood sugar self- measurement reagent for diabetes patients. The Seralyzer (apparatus and reagents) is a dry chemistry system for biochemical testing. However, pressure is exerted by manufacturers such as Fuji Film, Nagase Sankyo (Kodak), etc.

6. Conditions of Cooperation

1) Capital

The percentages of capital received are 45% from Sankyo, 45% from Miles Laboratories of the United States and 10% from Ono Yakuhin Kogyo.

2) Sales

There are joint sales by Sankyo and Ono Yakuhin Kogyo. Some of the pathophysiologic test equipment uses Sakura Seiki sales routes.

7. Development Trends

New products related to urinalysis testing, e.g., urine sediment standard preparation systems, urophanic leukocyte test strips, etc., are currently being marketed. Although the company would like to emphasize fields related to immunology in the future, there is also the relationship with Miles Laboratories of the United States and it is thought that the basic plan will take a little more time.

DAIICHI RADIOISOTOPE LABORATORIES, LTD.

1. Company Outline

Mail Address: 3-10-5 Nihonbashi, Chuo-ku, Tokyo 103
Phone: 03-272-1651
Fax: 03-272-4976
Established: December 1968
Representative: Osamu Ikeda, President
Capitalization: Yen 400 million
Employees: 370
Major Shareholders: Daiichi Seiyaku (65%), Daiichi Pure Chemical (35%)
Financial Results (Million Yen):

	Mar. 87	Mar. 88	Mar. 89
Sales	11,000	11,600	12,200
Profit	596	625	650

2. Sales of Diagnostic Division (Million Yen):

	Mar. 85	Mar. 86	Mar. 87	Mar. 88	Mar. 89
Diagnostic reagents	6,700	7,000	7,370	7,560	7,930
Test equipment	-	-	-	-	-
Others	2,900	3,200	3,630	4,040	4,270
Total	9,600	10,200	11,000	11,600	12,200

Note: All diagnostics are RIA (in-vitro) products and others are all RIA (in-vivo) products. Daiichi started marketing IgERAST for checking allergen in November 1989 as a non-RIA diagnostic where the company will put efforts.

3. Sales of Diagnostics by Area (Million Yen):

Test Area	Mar. 85	Mar. 86	Mar. 87	Mar. 88	Mar. 89
General	-	-	-	-	-
Haematological	-	-	-	-	-
Biochemical	-	-	-	-	-
Immunoserological	-	-	-	-	-
Microbiological	-	-	-	-	-
Control	-	-	-	-	-
RIA	6,700	7,000	7,370	7,560	7,930
Total	6,700	7,000	7,370	7,560	7,930

4. Rank and Characteristics in the Diagnostics Market

The company was established in 1968 as a business concerning RIA (in-vitro and in-vivo) diagnostics. This is the manufacturer second to Dainabot in RIA (in-vitro) and second to Japan Mediphysics in RIA (in-vivo).

However, non-RIA conversion has recently progressed in the diagnostics marketplace and there is a definite need to respond to this trend. This company also marketed an Ig ERAST kit as its first non-RIA effort in November 1989. It is thought that several non-RIA reagents will appear in the future.

5. Actual Sales of Top Five Products

unit (million yen)

rank	product	March 1989 (estimated)
1	Ultratechnekau [phonetic]	1,600
2	potassium citrate Ga67 (in-vivo)	1,100
3	Ig ERAST (in-vitro)	1,050
4	ferritin (in-vitro)	880
5	//beta//2-microglodulin (in-vitro)	850

6. Conditions of Cooperation

1) Capital

Although there was capital participation by Mallinckrodt at the start, Daiichi Seiyaku took charge in 1988. The capital percentages are currently 65% from Daiichi Seiyaku and 35% from Daiichi Kagaku Yakuhin.

Daiichi Kagaku Yakuhin is a 100% subsidiary of Daiichi Seiyaku and a diagnostics manufacturer (however, it does not have RIA products).

2) Sales

Import of France CIS, Canada Merck Frosst and United States Rohm & Haas Co. products are conducted.

7. Development Trends

Attention is turned to the development of circulatory system diagnostics in the RIA in-vivo products. It also appears that efforts related to tumors will be made from the long term viewpoint.

Development of tumor markers in RIA in-vitro products.

Completion of EIA products in the non-RIA field.

SANKYO CO., LTD.

1. Company Outline

Mail Address: 2-7-12 Ginza, Chuo-ku, Tokyo 104
Phone: 03-562-0411
Fax: 03-561-5409
Telex: J24838 DIASTASE
Established: March 1913
Representative: Yoshinori Kawamura, President
Capitalization: Yen 27,883 million
Employees: 5,979
Major Shareholders: Nippon Life Insurance (7.2%), Daiichi-Kangyo Bank (4.7%), Sumitomo Trust Bank (4.3%), etc.
Financial Results (Million Yen):

	Mar. 87	Mar. 88	Mar. 89
Sales	279,660	291,724	308,510
Profit	9,393	10,473	12,461

2. Sales of Diagnostic Division (Million Yen):

	Mar. 85	Mar. 86	Mar. 87	Mar. 88	Mar. 89
Diagnostic reagents	5,440	5,580	5,680	6,140	6,780
Test equipment	1,000	1,020	1,150	1,250	1,410
Others	450	420	425	500	550
Total	6,890	7,020	7,255	7,890	8,740

3. Sales of Diagnostics by Area (Million Yen):

Test Area	Mar. 85	Mar. 86	Mar. 87	Mar. 88	Mar. 89
General	3,080	3,100	3,100	3,100	3,150
Haematological	560	590	610	770	885
Biochemical	840	850	870	1,050	1,210
Immunoserological	550	570	630	720	830
Microbiological	0	0	0	0	0
Control	110	120	120	140	240
Pathology	300	350	350	360	465
Total	5,440	5,580	5,680	6,140	6,780

4. Rank and Characteristics in the Diagnostics Market

Actual sales which emphasized urinalysis reagents handled by Miles-Sankyo gained influence from the time of entry into the market in 1973.

Sales have also recently expanded to other fields such as biochemical testing, blood testing, etc., so that the percentage of urinalysis reagents sales is only 50%. Attention will be turned in the future to the immunoserological field and blood testing field, and sales expansion is targeted.

5. Actual Sales of Top Five Products

unit (million yen)

rank	product	March 1989 (estimated)
1	general testing	3,150
2	reagents associated with blood coagulation	820
3	Glucostix	1,100
4	pathophysiologic test reagents	360
5	pregnancy diagnostics	270

6. Conditions of Cooperation

1) Capital

45% Sankyo, 45% Miles Laboratories, 10% Ono Yakuhin Kogyo.

2) Sales

Sales of Miles-Sankyo products (general test reagents, TDM systems, biochemistry, etc.).

Sales of Nittobo products (blood coagulation test reagents by synthetic substrate method).

Hitachi Seisakusho: commission production of blood coagulation meters and ultrasound diagnostic apparatus.

Sankyo Zoki: sale of biochemical test reagents such as LAP, -GTP, CAP, etc., produced by this company.

Organone: sale of pregnancy diagnostics and HB associated reagents.

7. Development Trends

Expansion of products in the blood coagulation and immune sera fields. A complete automatic type of EI apparatus is expected in particular to be marketed within 1 to 2 years.

DAIICHI PURE CHEMICALS CO., LTD.

1. Company Outline

Mail Address: 3-13-5 Nihonbashi, Chuo-ku, Tokyo 103
Phone: 03-272-0671
Fax: 03-272-0635
Telex: J25495 DAICHEM
Established: July 1947
Representative: Tomomichi Sato, President
Capitalization: Yen 960 million
Employees: 770
Major Shareholder: Daiichi Seiyaku (100%)
Financial Results (Million Yen):

	Mar. 87	Mar. 88	Mar. 89
Sales	15,376	16,645	18,426
Profit	352	304	936

2. Sales of Diagnostic Division (Million Yen):

	Mar. 85	Mar. 86	Mar. 87	Mar. 88	Mar. 89
Diagnostic reagents	5,100	5,200	5,750	6,100	6,860
Test equipment	50	50	50	50	50
Others	-	-	-	-	-
Total	5,150	5,250	5,800	6,150	6,910

3. Sales of Diagnostics by Area (Million Yen):

Test Area	Mar. 85	Mar. 86	Mar. 87	Mar. 88	Mar. 89
General	215	140	65	70	70
Haematological	400	450	560	680	750
Biochemical	3,400	3,500	3,900	4,000	4,400
Immunoserological	830	840	900	1,000	1,200
Microbiological	90	100	150	175	190
Control	165	170	175	175	250
RIA	-	-	-	-	-
Total	5,100	5,200	5,750	6,100	6,860

4. Rank and Characteristics in the Diagnostics Market

This is a manufacturer that emphasizes reagents for automated analysis of biochemical tests. However, sales are also gradually expanding into the fields of immune sera and those associated with blood coagulation. The company succeeded in producing an apolipoprotein kit before others in 1982.

5. Actual Sales of Top Five Products

unit (million yen)

rank	product	March 1989 (estimated)
1	biochemical autoreagents	3,080
2	Test Time (blood coagulation)	750
3	bile acid	680
4	apolipoprotein	450
5	EMIT (TDM)	250

6. Conditions of Cooperation

1) Capital

Daiichi Yakuhin: 100% capital.

2) Sales

Import sales of blood coagulation factor reagents (Kabi Co.).

Import sales of TDA reagents (Sever Co. of the United States).

7. Development Trends

Attention is turned to diagnostics related to infectious disease (herpes antigen, chlamydia antigen, rotavirus antigen).

There is cooperation with the Chiron Company of the United States in the development, production and exclusive sales agent of DNA probe reagents. Two million dollars in research and development funds are expected to be supplied to Kairon in the next 5 years. Attention will be turned to the development of type A, type B and non-A non-B hepatitis virus, etc.

NISSUI PHARMACEUTICAL CO., LTD.

1. Company Outline

Mail Address: 2-11-1 Sugamo, Toshima-ku, Tokyo 170
Phone: 03-918-8161
Fax: 03-918-4515
Telex: 2722341 NSYAKU J
Established: April 1935
Representative: Yasuaki Kobayashi, President
Capitalization: Yen 880 million
Employees: 380
Major Shareholder: Nippon Suisan (78%)
Financial Results (Million Yen):

	Mar. 87	Mar. 88	Mar. 89
Sales	9,755	10,094	10,366
Profit	308	457	578

2. Sales of Diagnostic Division (Million Yen):

	Mar. 85	Mar. 86	Mar. 87	Mar. 88	Mar. 89
Diagnostic reagents	5,300	5,700	6,000	6,300	6,450
Test equipment	-	-	-	-	-
Others	800	800	800	850	850
Total	6,100	6,500	6,800	7,150	7,300

3. Sales of Diagnostics by Area (Million Yen):

Test Area	Mar. 85	Mar. 86	Mar. 87	Mar. 88	Mar. 89
General	-	-	-	-	-
Haematological	-	-	-	-	-
Biochemical	1,000	1,000	950	950	1,050
Immunoserological	1,000	1,200	1,400	1,500	1,500
Microbiological	3,000	3,200	3,300	3,480	3,500
Control	300	300	350	370	400
RIA	-	-	-	-	-
Total	5,300	5,700	6,000	6,300	6,450

4. Rank and Characteristics in the Diagnostics market

The company was founded as a marine products research facility under the influence of Nippon Suisan. Production and sale of SS agar medium and various media for bacterial testing began in 1952, and the company is currently the largest medium manufacturer.

In addition to reagents for bacterial testing, attention is currently to expanding into the biochemical field and the company is becoming a major diagnostics manufacturer.

5. Actual Sales of Top Five Products

unit (million yen)

rank	product	March 1989 (estimated)
1	raw media	800
2	immunoturbidometry reagents	710
3	sensitivity disks	660
4	powdered media	500
5	biochemical autoreagents	450

Although many of the top products are related to bacterial testing, there are also actual results on reagents for automated analysis by immunoturbidimetry. The market is expanding rapidly through entry into automatic chemical analyzers. Representative test items include CRP, IgG, ·A ·M, complements C_3, C_4, etc.

6. Conditions of Cooperation

1) Capital

Nippon Suisan 78% capital.

2) Sales

Sale of Showa Yakuhin sensitivity disks.

Introduction of Tosoh EIA fully automatic equipment AIAl2OO.

7. Development Trends

Expansion of test items by immunoturbidimetry.

Development of EIA diagnostics.

Development of diagnostic systems for items related to infectious disease by new methods.

An exclusive sales contract within Japan was made with Gene-Track System of the United States in December 1989 for DNA probe diagnostic systems (diagnostics and equipment). Commercialization is on a scale of 4 to 5 years hence.

5 Canadian Contacts for Exporters to Japan

External Affairs And International Trade Canada

Japan Trade Development Division (PNJ)
Asia Pacific North Bureau
External Affairs and International Trade Canada
Lester B. Pearson Building
125 Sussex Drive
Ottawa, Ontario
K1A 0G2
Tel: (613) 995-1281
Telex: 053-3745
Fax: (613) 996-4309

International Trade Centres

British Columbia
International Trade Centre
P.O. Box 11610
900 – 650 West Georgia Street
Scotia Tower
Vancouver, British Columbia
V6B 5H8
Tel: (604) 666-1444
Telex: 0451191
Fax: (604) 666-8330

Alberta
International Trade Centre
Canada Place
Suite 540
9700 Jasper Avenue
Edmonton, Alberta
T5J 4C3
Tel: (403) 495-2944
Telex: 0372762
Fax: (403) 495-4507

International Trade Centre
Suite 1100
510 – 5th Street Southwest
Calgary, Alberta
T2P 3S2
Tel: (403) 292-6660
Fax: (403) 292-4578

Saskatchewan
International Trade Centre
6th Floor
105 – 21st Street East
Saskatoon, Saskatchewan
S7K 0B3
Tel: (306) 975-5925
Telex: 0742742
Fax: (306) 975-5334

Manitoba
International Trade Centre
8th Floor
330 Portage Avenue
P.O. Box 981
Winnipeg, Manitoba
R3C 2V2
Tel: (204) 983-8036
Telex: 0757624
Fax: (204) 983-2187

Ontario
International Trade Centre
4th Floor
Dominion Public Building
1 Front Street West
Toronto, Ontario
M5J 1A4
Tel: (416) 973-5053
Telex: 06524378
Fax: (416) 973-8161

Quebec
International Trade Centre
Stock Exchange Tower
800 Victoria Square
Room 3800
P.O. Box 247
Montreal, Quebec
H4Z 1E8
Tel: (514) 283-8185
Telex: 05560768
Fax: (514) 283-3302

New Brunswick
International Trade Centre
Assumption Place
770 Main Street
P.O. Box 1210
Moncton, New Brunswick
E1C 8P9
Tel: (506) 857-6452
Telex: 0142200
Fax: (506) 857-6429

Nova Scotia
International Trade Centre
Central Guaranty Trust Building
1801 Hollis Street
P.O. Box 940, Station M
Halifax, Nova Scotia
B3J 2V9
Tel: (902) 426-7540
Telex: 01922525
Fax: (902) 426-2624

Prince Edward Island
International Trade Centre
Confederation Court Mall
134 Kent Street, Suite 400
P.O. Box 1115
Charlottetown, P.E.I.
C1A 7M8
Tel: (902) 566-7400
Telex: 01444129
Fax: (902) 566-7450

Newfoundland and Labrador
International Trade Centre
90 O'Leary Avenue
P.O. Box 8950
St. John's, Newfoundland
A1B 3R9
Tel: (709) 772-5511
Telex: 0164749
Fax: (709) 772-2373

Industry, Science and Technology Canada

Business Centre
Industry, Science and Technology Canada
235 Queen Street
Ottawa, Ontario
K1A 0H5
Tel: (613) 995-5771

Northwest Territories
Industry, Science and Technology Canada
Precambrian Building
P.O. Bag 6100
Yellowknife, Northwest Territories
X1A 2R3
Tel: (403) 920-8578
Fax: (403) 873-6228
AES: (403) 920-2618

Yukon
Industry, Science and Technology Canada
108 Lambert Street
Suite 301
Whitehorse, Yukon
Y1A 1Z2
Tel: (403) 668-4655
Telex: 0142200
Fax: (403) 668-5003

Appendix 1-1) Total Market Size by Test Field

Test Field	1985	1986	1987	1988	1989 (est)
General Test					
Test number ('000)	710,440	741,910	791,370	835,500	900,000
Value (million yen)	7,800	8,250	8,800	9,300	10,000
Haematological Test					
Test number ('000)	1,164,470	1,210,510	1,258,990	1,313,310	1,400,000
Value (million yen)	8,500	9,000	9,700	10,300	11,000
Biochemical Test					
Test number ('000)	1,866,960	1,952,930	2,150,000	2,345,000	2,544,000
Value (million yen)	39,000	41,500	45,000	48,000	51,100
Immunoserological Test					
Test number ('000)	335,000	345,000	358,400	381,700	411,500
Value (million yen)	34,000	38,000	44,800	50,000	56,000
RIA (in-vitro)					
Test number ('000)	64,500	69,250	75,500	79,200	79,900
Value (million yen)	28,500	30,500	32,500	33,500	33,850
Microbiological Test					
Test number ('000)	112,200	113,050	116,400	119,570	125,000
Value (million yen)	9,900	10,735	11,630	12,660	13,900
Control					
Value (million yen)	4,500	4,800	5,000	5,500	6,000
Total					
Test number ('000)	4,244,570	4,432,650	4,750,660	5,074,280	5,460,400
Value (million yen)	132,200	142,785	157,430	169,260	181,850
Change over the previous year (%)					
Test number	-	104.4	107.2	106.8	107.6
Value	-	108.0	110.3	107.5	107.4
Market Share (%)					
General	5.9	5.8	5.6	5.5	5.5
Haematological	6.4	6.3	6.2	6.1	6.0
Biochemical	29.5	29.1	28.6	28.4	28.1
Immunoserological	25.7	26.6	28.5	29.5	30.8
RIA	21.6	21.4	20.6	19.8	18.6
Microbiological	7.5	7.5	7.4	7.5	7.6
Control	3.4	3.4	3.2	3.2	3.3
Total	100	100	100	100	100

A. Definition of Clinical Tests

1) Types of tests

In-vivo test:	diagnostic information obtained by directly taking various data from the body (monitor, imaging diagnostics, etc.) Excluded from the subjects investigated at this time.
In-vitro tests:	Diagnostic information obtained by taking a sample (part of the body) and analyzing its components. Of the aforementioned, in-vitro tests are called clinical tests.

2) Definition of Drugs used in Clinical Tests

Legally, drugs for clinical tests are categorized as diagnostic drugs. Their place among diagnostic drugs is shown below:

In-vivo diagnostic drugs:	contrast media, RIA (in-vivo). Excluded from the subjects investigated this time.
In-vitro diagnostic drugs:	diagnostics (in-vitro)

3) Divisions of Clinical Test Fields

Clinical tests are divided into fields based on several criteria. The standards for actual divisions are by the type of specimen, the substances determined, and the determination method.

B. Definition of each test field

Test field types	Type of specimen	Determination method	Determined properties and
General test pH,	Urine, feces,	Biological method	Sugar, protein, urobilinogen,
	spinal fluid	Biochemical method	bilirubin, ketones, occult blood, phenyl ketones, nitrites, specific gravity, appearance, etc.
Haematological	Blood cells, plasma	Electrical resistance, optical Morphological observation Activity determination	Blood cell counts, coagulation, differential counts, fibrinolytic substance activity
Biochemical	Serum	Biochemical method	Enzymes, lipids, sugars, nitrogen compounds, hormones inorganic substances
Immunoserological	Serum	Antigen-antibody reaction	Blood type, autoantibody, tumor markers, hormones, bacterial antibody, viral antigen, viral antibody, plasma proteins, TDM
RIA (in-vitro)	Serum	Antigen-antibody reaction (radioisotope)	Hormones, tumor markers, viruses, TDM, etc.
Microbiological	Blood, urine, sputum, spinal fluid, feces, pharyngeal and nasal secretions, pus, genital secretions	Isolated cultivation Identification (biochemical) Sensitivity test	Bacteria
Control	-	-	The control is not a diagnostic drug and is for controlling determination devices. The types are control serum for automated chemical analysis, control blood cells for blood cell counters, and control plasma for blood coagulation devices.

C. Number and Cost of Tests

C-1) Number of Tests

1) General Tests

In urinalyses, which account for the majority of general tests, one piece of test paper can be used to determine 1 to 7 items. In this case, the number of tests is not the number of pieces of test paper. When 7 items are determined with 1 piece of test paper, the number of tests is counted as 7.

2) Haematological Tests

There are test items that can be calculated without using a reagent when determining blood cell counts and these are included in the number of tests.

3) Biochemical Tests

Biochemical tests, the unit price of manual method and automated methods vary by 2-fold to 5-fold. The number of tests is the total number performed by the two methods.

4) Immunoserological Tests

There are cases of double determinations with quantitative determination in immunoassay using immune serum. The number of tests was calculated as two tests in the case of double determinations.

5) RIA (in-vitro)

The number of assays and the number of tubes used do not coincide in RIA because of double determinations and problems with half-life. The number of tests in this case is the number of tubes that were used.

6) Microbiological Tests

The number of tests was the number of culture dishes in isolated cultivation, the number of culture dishes and the number of simple fixation kits in fixation tests, the number of culture dishes and test tubes in sensitivity tests, the number of bottles for blood cultivation in blood cultivation tests, and the number of culture dishes and the number of urine quantitative determination kits in urine quantitative determinations.

7) Control

Since the purpose for which the control is used does not apply to the general concept of the number of tests, the number of items used in control tests was excluded from the total number of tests.

C-2) Cost

The market on a cost basis was calculated as the manufacturer delivery base in all test fields.

D. General tendency of each test field

1) General laboratory tests

- Urinalysis accounting for 80% of all general clinical laboratory tests is conducted using strips of test paper and those capable of measuring multiple items simultaneously with one piece are becoming more predominant in the market. However, there have been no new basic developments that add up new test items in this field of testing, and growth has slowed to a mere 2% increase per year.

- In fecal tests, occult blood tests are attracting considerable attention. The trend in this area is a shift from conventional haemoglobin measurement based on peroxidase activity towards measurement of human haemoglobin by means of more specific antigen-antibody reactions. This test permits screening for large bowel cancer without the necessity of dietary restrictions. Considerable growth in this market is anticipated.

2) Haematological tests

- The market of the blood cell count and classification in the haematological test is essentially based on the consumption of staining solutions and diluents with low added value. Thus the market is small and in the state of saturation despite the fact that the number of tests is large. Therefore less attention is being drawn to this area.

- In contrast, unit value per test is relatively high for the system regarding blood coagulation and fibrinolysis and markets are large. These areas are thus attracting considerable attention. There is a shift away from methods involving conventional measurement of activity, with a trend towards newer forms of antigen qualification. New test items include TPA, protein C and FDPD dimer, with considerable market growth anticipated in this area.

  However, there are as yet few doctors specializing in blood coagulation and fibrinolytic tests, and the tests themselves are still considered "special tests". Market growth in this area will thus require education in the clinical sector.

3) Biochemical tests

- The area of biochemical testing accounts for the largest market within the clinical laboratory test field. Expansion of this market may be said to have contributed a great deal to total market growth.

- This is because popularity of automated chemical analyzers, which can conduct multiple measurements on large number of samples has increased, resulting in a rapid jump in number of tests performed.

- However, negative factors are also affecting the market in this area. These include the difficulty of expansion to include new test items, reduction in health insurance ratings, reductions in reagent price due to rounding, and reductions in the amount of reagent used under fully automated operation. On balance, the monetary-base market is expanding at only slightly over 1% annually.

- Items for measurement of particular attention include the diabetes-associated fructosamine and pancreatitis-associated amylase.

- As an innovating measurement system, there is great interest in "dry chemistry" which permits measurement of test items using whole blood as the sample.

4) Immunoserological tests

- Until recently, immunoserological tests used to center around qualitative tests based primarily on the agglutination method, and generally be performed manually. However, new highly sensitive quantitative methods such as nephelometric immunoassay (NIA), latex agglutination immunoassay, EIA, FIA, and CLIA have now been developed. Progress is also being made in automation. In clinical laboratory testing, this field is today the focus of greatest interest.

- With regard to immunoserological tests, factors influencing market expansion include the trend from qualitative to quantitative testing, the trend from RIA towards NONRIA, and the development of new test items.

- When viewed according to test areas, markets are getting mature for plasma proteins and cancer markers. Future market expansion is anticipated in the areas of hormones and infectious diseases.

- Among the NONRIA-type assay methods, EIA, FIA and CLIA all offer the potential for highly sensitive measurements. Considerable interest is currently focused on the question of which will become the predominant measurement method.

5) RIA (In-vitro)

On the whole, there has been a tendency toward a reduction in the RIA market because of the fact that radioactive substances are used and therefore, facilities where RIA can be performed are limited, the problem with waste treatment, etc. However, RIA is a very accurate and sensitive quantitative determination method and new test items are often used in RIA. Moreover, hormone tests, which take a leading part in the test items of RIA, are special tests and the weight of hormone tests performed at test centers is high in terms of the number of tests. In addition, it is still not possible to handle large numbers of specimens in a fully automated manner by NONRIA. Therefore, it appears that growth of 3% will be maintained for at least 2 to 3 years.

6) Microbiological test

Microbiology involves the processes of single staining, Gram's staining, isolated cultivation, identification, and sensitivity tests. All are manual methods. It takes at least 2 to 3 days, and in slower cases, 1 to 2 months, for cultivation. Therefore, of the clinical tests, automation of microbiology has been delayed. As a result, the findings of these tests are rarely directly involved in treatment.

In terms of the trends in products, there has been a change from powder media to live media. Moreover, there has been a change from conventional identification using biochemical techniques with the development of simple identification kits that can now identify several bacteria from one group at the same time. Moreover, attention is also being focused on a market for direct identification kits for uncultivated bacteria themselves by antigen-antibody reactions.

7) Control

The market for controls has grown with automation of tests. However, controls are either limited to conventional biochemical tests and haematology, and also a control market for immunoserological tests is being formed with automation of these tests.

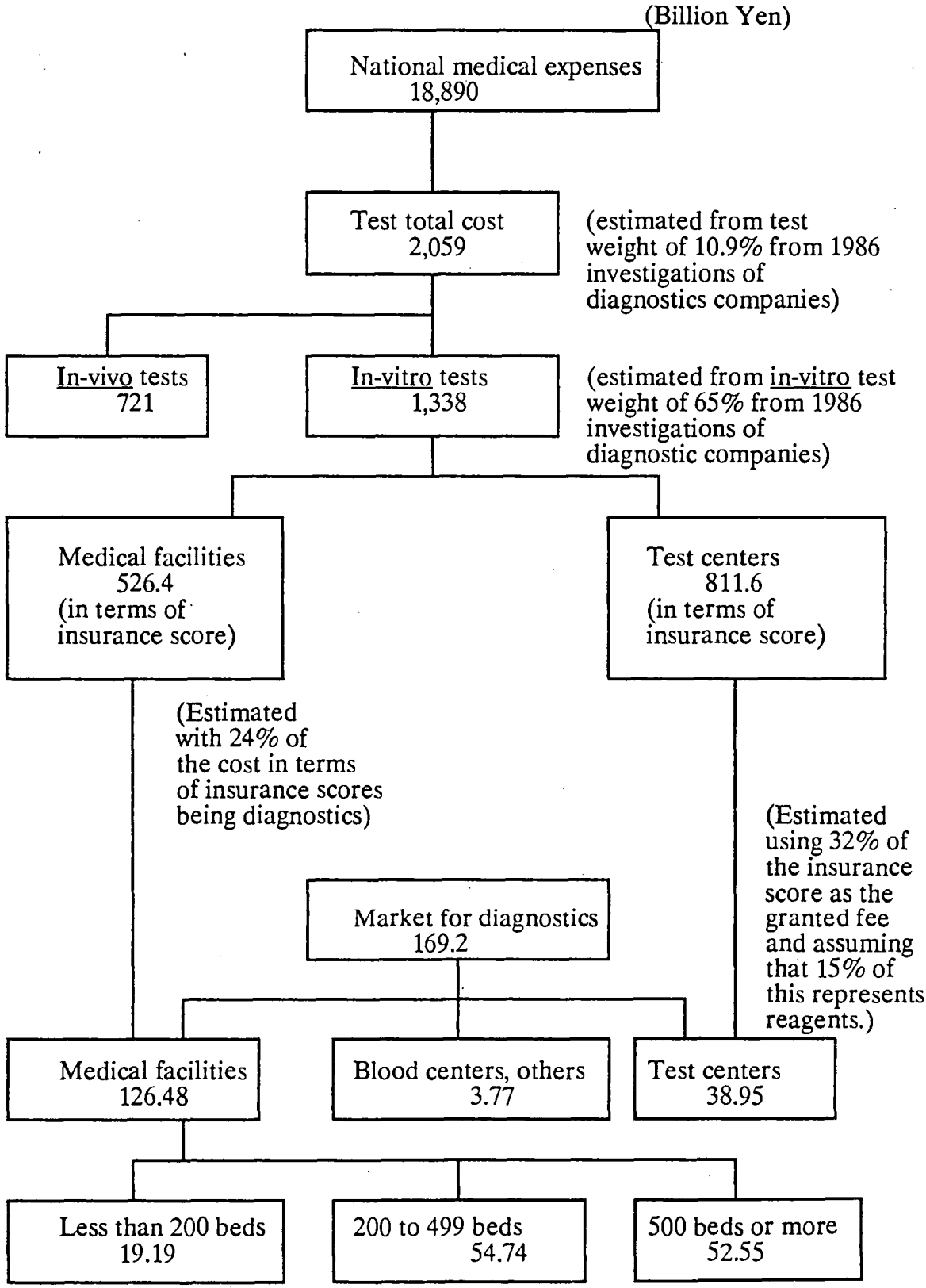
Appendix 1-2) Total Market Size by Testing Institution (1988)

Unit: million yen, (share in %)

Test Field	Hospital			Test Center	Blood Center and others*	Total
	199 beds or less	200-499 beds	500 beds or more			
General	2,855 (30.7)	3,485 (37.5)	2,640 (28.4)	320 (3.4)	-	9,300 (100)
Haematological	2,215 (21.5)	2,875 (27.9)	3,545 (34.4)	1,665 (16.2)	-	10,300 (100)
Biochemical	8,080 (16.8)	15,860 (33.0)	11,920 (24.8)	11,100 (23.1)	1,040 (2.3)	48,000 (100)
Immunoserological	2,950 (5.9)	16,650 (33.3)	16,050 (32.1)	12,500 (25.0)	1,850 (3.7)	50,000 (100)
RIA	770 (2.3)	9,895 (29.5)	11,850 (35.4)	10,820 (32.3)	165 (0.5)	33,500 (100)
Microbiological	1,150 (9.1)	3,450 (27.3)	4,490 (35.5)	2,760 (21.8)	810 (6.3)	12,660 (100)
Control	885 (16.1)	1,865 (33.9)	1,435 (26.1)	1,210 (22.0)	105 (1.9)	5,500 (100)
Total	18,905 (11.2)	54,080 (31.9)	51,930 (30.7)	40,375 (23.9)	3,970 (2.3)	169,260 (100)

*Note: Others include prefectural sanitary laboratories and national laboratories.

Appendix 1-3) Diagnostics Market Structure Based on National Medical Expenses ('88 estimates)



Appendix 2-1) Market Size of 30 Major Test Items

No	Test Item	(Million Yen) 1987	1988	1989(est)	Test Area
1	CEA	4,995	5,220	5,450	cancer marker, immunology, RIA
2	Syphilis	3,774	3,891	4,010	infectious disease, immunology
3	HBs antigen	3,800	3,875	3,920	infectious disease, immunol., RIA
4	AFP	3,620	3,750	3,869	cancer marker, immunology, RIA
5	Total cholesterol	3,540	3,640	3,740	lipid, biochemistry
6	Triglyceride	3,100	3,285	3,450	lipid, biochemistry
7	CA19-9	2,160	2,857	3,360	cancer marker, Immunology, RIA
8	HD cholesterol	2,900	3,075	3,275	lipid, biochemical
9	Amylase	2,850	3,050	3,250	enzyme, biochemical
10	ASO	2,862	2,991	3,200	infectious disease, immunology
11	CRP	2,640	2,780	2,900	inflammation marker, immunology
12	HBs antibody	2,679	2,760	2,840	infectious disease, immunol., RIA
13	FDP	2,300	2,340	2,460	coagulation, haematology
14	beta2-microglobulin	2,050	2,254	2,433	cancer marker, immunology, RIA
15	Pregnancy test	2,380	2,400	2,420	hormone, immunology
16	gamma-GTP	2,310	2,370	2,416	enzyme, biochemical
17	Free fatty acid	2,300	2,350	2,400	lipid, immunology
18	IgG,A,M	2,050	2,180	2,320	plasma protein, immunology
19	ATL	1,638	2,020	2,150	infectious disease, immunology
20	beta-lipoprotein	1,780	1,890	1,982	protein, biochemical
21	Glyco-haemoglobin	1,845	1,849	1,902	lipid, biochemical
22	Ferritin	1,520	1,700	1,845	cancer marker, immunol., RIA
23	RA	1,660	1,750	1,826	rheumatoid factor, immunology
24	HIV	1,620	1,681	1,743	infectious disease, immunology
25	Phospholipid	1,390	1,490	1,575	lipid, biochemical
26	HCG (quantitation)	1,385	1,467	1,550	hormone, immunology, RIA
27	CPK	1,320	1,420	1,520	enzyme, biochemical
28	BuN	1,200	1,260	1,316	nitrogen, biochemical
29	T_4	1,350	1,260	1,260	hormone, immunology, RIA
30	GOT	1,185	1,210	1,235	enzyme, biochemical
Total		70,203	74,065	77,617	

- The 30 major categories listed above hold 43.8% of the market. As the test categories total approximately 400, about 10% of test items share more than 40% of the market.

- The 30 categories can be classified as follows: 5 categories are cancer markers, 6 are infectious disease tests, 12 are biochemical, 3 are hormone, 3 are plasma protein and one is blood coagulation.

- Since the 30th item has a more than 1.2 billion yen market, it is estimated that the number of test items which have a more than one billion yen market ranges from 35 to 40. This one billion yen value can be a kind of criteria for major test items.

Appendix 2-2) Market Size of Selected Test Items

1) Value

(Million Yen)

Test Item	1986	1987	1988	1989
A. Cancer Markers				
A-1. KMO-1	-	13	42	84
A-2. CA-50	-	-	18	70
A-3. ST439	-	-	-	-
A-4. BFP	-	-	-	-
A-5. DUPAN-2	-	0	171	290
A-6. SLX	-	-	80	120
A-7. TPA	424	444	484	532
A-8. SCC antigen	330	420	510	612
A-9. NSE	38	158	241	312
A-10.CA19-9	1,620	2,160	2,857	3,360
A-11.CA125	331	509	749	1,032
A-12.CA15-3	37	72	148	270
A-13.IAP	206	248	388	465
A-14.gamma-Sm	54	108	162	162
A-15.Elastase-1	780	975	1,105	1,215
A-16.PRG	-	-	4	20
B. Diabetes				
B-1. Haemoglobin A_1	1,014	533	283	228
B-2. Haemoglobin A_{1c}	936	1,312	1,566	1,674
B-3. Urine albumin	9	55	156	270
B-4. Fructosamine	-	-	364	539
B-5. 1,5-AG	-	-	-	-
C. Liver Diseases				
C-1. Guanase	42	84	123	147
C-2. ADA	60	100	140	180
C-3. LCAT	90	100	110	121
C-4. HCV	-	-	-	-
D. Kidney Diseases				
D-1. NAG	450	500	540	590
D-2. AAP	-	2	5	7
E. Others				
E-1. Immune complex	22	23	26	28
E-2. Interferon	40	30	45	50
E-3. Interleukin	-	15	14	15

2) Number of Tests

(Thousand)

Test Item	1986	1987	1988	1989
A. Cancer Markers				
A-1. KMO-1	-	30	80	180
A-2. CA-50	-	-	25	100
A-3. ST439	-	-	-	-
A-4. BFP	-	-	-	-
A-5. DUPAN-2	-	0	300	510
A-6. SLX	-	-	48	200
A-7. TPA	837	900	1,000	1,100
A-8. SCC antigen	550	700	850	1,020
A-9. NSE	60	250	380	494
A-10.CA19-9	2,700	3,600	4,800	5,600
A-11.CA125	550	850	1,248	1,720
A-12.CA15-3	60	120	148	450
A-13.IAP	530	640	1,000	1,200
A-14.gamma-Sm	100	200	300	300
A-15.Elastase-1	1,200	1,500	1,700	1,870
A-16.PRG	-	-	5	20
B. Diabetes				
B-1. Haemoglobin A_1	3,120	1,640	870	700
B-2. Haemoglobin A_{1c}	4,860	6,560	7,830	8,390
B-3. Urine albumin	20	110	394	600
B-4. Fructosamine	-	-	2,700	4,800
B-5. 1,5-AG	-	-	-	-
C. Liver Diseases				
C-1. Guanase	600	1,200	1,750	2,100
C-2. ADA	1,300	2,200	3,100	4,000
C-3. LCAT	160	178	196	216
C-4. HCV	-	-	-	-
D. Kidney Diseases				
D-1. NAG	1,880	2,080	2,290	2,520
D-2. AAP	-	17	41	61
E. Others				
E-1. Immune complex	142	155	170	187
E-2. Interferon	36	27	41	45
E-3. Interleukin	-	11	10	11

Appendix 2-3) Test Methods

Test Method / Test Item	EIA	RIA	Latex	i.n.	SRID	RPHA	UV	c.m.	Column	a.c.	HPLC	e.p.	FIA
A. Cancer Markers													
A-1. KMO-1	x					x							
A-2. CA-50	x											x	
A-3. ST439	xx												
A-4. BFP	x												
A-5. DUPAN-2	x												
A-6. SLX		x											
A-7. TPA		x											
A-8. SCC antigen		x											
A-9. NSE	x	x											
A-10.CA19-9	x	x											
A-11.CA125	x	x											
A-12.CA15-3		x											
A-13.IAP				x		x							
A-14.gamma-Sm	x												
A-15.Elastase-1		x											
A-16.PRG	x												
B. Diabetes													
B-1. Haemoglobin A_1									x	x		x	
B-2. Haemoglobin A_{1c}									x	x	x		
B-3. Urine albumin		x	x	x									
B-4. Fructosamine							x						
B-5. 1,5-AG									xx				
C. Liver Diseases													
C-1. Guanase							x						
C-2. ADA							x						
C-3. LCAT								x					
C-4. HCV	x												
D. Kidney Diseases													
D-1. NAG								x					
D-2. AAP								x					
E. Others													
E-1. Immune complex	x					x							
E-2. Interferon	x	x											
E-3. Interleukin	x												

Note: 1) i.n.:immunonephelometry; c.m.:colorimetry; a.c.:affinity column; e.p.:electrophoresis
2) x: on the market, xx: under development

Appendix 2-4) Detectable Diseases by Cancer Markers

Item Number / Disease	A-1	A-2	A-3	A-4	A-5	A-6	A-7	A-8	A-9	A-10	A-11	A-12	A-13	A-14	A-15	A-16
Digestive/Respiratory Organ Cancers																
Hepatoma	b	b			b		a			c	c	d	d		d	
Gallbladder cancer	b	a	b		c		a			c	c		a			
Esophagus cancer		d	d			d		c	c		d		a		d	
Colon cancer	b	c	c		d		b			c	d	d	b		d	
Pancreas cancer		a	a	b		b	b	a			a	b	c	a		b
Stomach cancer	d	d			d		b			c	c		b		d	
Lung cancer		d			c	d	c	b	c	a	d	d	d	a		
Urinary/Genital Organ Cancers																
Mammary cancer	d		c		d		c			d	c	b	d			b
Uterus cancer	d			c			b	c		c	d	c	c			
Ovary cancer	b			b		b	a			d	a	c	b			
Bladder cancer				c			b					d	a			
Prostate gland cancer					b			b					c	c	b	
Kidney cancer				c								d	a			
Blood System																
Leukemia							d						a			
Non-cancer Diseases																
Hepatitis		d			d		a			d	d		d		d	
Hepatocirrhosis			a			d		c			d	d			d	
Pancreatitis	d	d			d		d			d					a	
Kidney failure					d		a			d					c	
Hysteromyoma	c							d		d	d					
Oophoroma	b							d		c	c		d			

(Note) a: more than 70% positivity
b: more than 50%
c: more than 30%
d: less than 30%

A-1: KMO-1 A-2: CA-50
A-3: ST439 A-4: BFP
A-5: DUPAN-2 A-6: SLX
A-7: TPA A-8: SCCA antigen
A-9: NSE A-10: CA19-9
A-11: CA125 A-12: CA15-3
A-13: IAP A-14: gamma Sm
A-15: Elastase-1 A-16: PGR

Appendix 2-5) Infectious Disease Diagnostics

1) Market Size Changes

(Million Yen)

Test Area	1985	1986	1987	1988	1989(est)
Bacteria	9,900	10,735	11,630	12,660	13,900
Immunological Bacteria	553	627	675	730	800
Direct kit	63	258	336	473	647
Virus antibody	5,446	7,345	9,224	9,884	10,230
Virus antigen	4,337	4,631	4,856	5,254	5,562
Immunological	6,450	6,780	7,092	7,343	7,730
Total	26,749	30,376	33,813	36,344	38,869

Note: "Immunological Bacteria" means bacteria test doing a separation culture. "Immunological" includes tests for syphilis, ASO, mycoplasma, Widal's reaction and Weil-Felix reaction.

2) Change of Market Share (%)

	1985	1986	1987	1988	1989
Bacteria	37.1	35.3	34.3	34.8	35.7
Bacteria with immunology	2.0	2.1	2.0	2.0	2.1
Direct kit	0.2	0.2	1.0	1.3	1.7
Virus antibody	20.4	24.2	27.3	27.2	26.3
Virus antigen	16.2	15.2	14.4	14.5	14.3
Immunological	24.1	22.4	21.0	20.2	19.9
Total	100	100	100	100	100

Appendix 2-6) Outline of Bacteria Test Market

1) Market size by test item

(Million Yen)

	1985	1986	1987	1988	1989
Separation culture	3,569	3,795	4,046	4,329	4,740
Identification	2,231	2,655	3,121	3,672	4,180
Sensitivity	2,488	2,591	2,687	2,800	3,000
Urine determination	970	1,020	1,071	1,122	1,210
Blood culture	432	456	480	504	530
Anaerobic bacteria	210	218	225	233	240
Total	9,900	10,735	11,630	12,660	13,900

2) Market share by test item (%)

	1985	1986	1987	1988	1989
Separation culture	36.1	35.4	34.8	34.2	34.1
Identification	22.5	24.7	26.8	29.0	30.1
Sensitivity	25.1	24.1	23.1	22.1	21.6
Urine determination	9.8	9.5	9.2	8.9	8.7
Blood culture	4.4	4.2	4.1	4.1	3.8
Anaerobic bacteria	2.1	2.0	1.9	1.8	1.7
Total	100	100	100	100	100

3) Market size by product in 1988

-Biological culture medium	4,770 million yen	(37.7%)
-Simple identification kit	3,583	(28.3%)
-Sensitivity disc	1,692	(13.4%)
-Powder medium	1,128	(8.9%)
-Urine determination kit	750	(5.9%)
-Blood culture bottle	504	(4.0%)
-Anaerobic bacteria gas pack	233	(1.8%)
Total	12,660	(100%)

4) Market share by company in 1988

Biological culture medium		
	Eiken Chemical	21.8%
	Japan Becton-Dickinson	20.8%
	Nissui Pharmaceutical	16.7%
	Kyokuto Pharmaceutical	10.0%
	Sanko Junyaku	6.9%
	Others	23.8%
Simple identification kit		
	Nippon Roche	26.4%
	Eiken Chemical	24.7%
	Aska Diagnostics	24.3%
	Nissui Pharmaceutical	12.0%
	Japan Becton-Dickinson	9.9%
	Others	2.7%
Sensitivity Disc		
	Nissui Pharmaceutical	38.4%
	Eiken Chemical	36.0%
	Others	25.6%
Powder medium		
	Nissui Pharmaceutical	43.9%
	Eiken Chemical	33.8%
	Japan Becton-Dickinson	12.7%
	Kyokuto Pharmaceutical	5.0%
	Others	4.6%
Urine determination kit		
	Nissui Pharmaceutical	38.0%
	Eiken Chemical	22.5%
	Nippon Roche	10.0%
	Daiichi Pure Chemical	2.5%
	Others	23.5%
Blood culture bottle		
	Nippon Roche	42.0%
	Eiken Chemical	22.5%
	Japan Becton-Dickinson	13.1%
	Others	22.5%
Anaerobic bacteria gas pack		
	Japan Becton-Dickinson	44.4%
	Kanto Chemical	32.0%
	Others	23.6%

Appendix 2-7) Outline of Immunological Bacteria Test Market

1) Change of market size

(Million Yen)

Kind of Product	1985	1986	1987	1988	1989
Identification kit	143	212	255	305	370
Antiserum	410	415	420	425	430
Total	553	627	675	730	800

2) Market by test item

(Million Yen)

Test Item	1985	1986	1987	1988	1989
Streptococcus	46	60	72	86	105
Gonococcus	5	10	14	20	30
Fungus	32	40	46	52	60
Staphylococcus	18	30	36	43	50
E. coli	14	25	30	35	40
Pneumococcus	17	30	36	43	50
Meningococcus	3	5	7	10	15
Influenza	8	12	14	16	20
Antiserum	410	415	420	425	430
Total	553	627	675	730	800

3) Market share by company in 1988

Streptococcus		
	Eiken Chemical	34.0%
	Shionogi	29.4%
	Syntech	18.6%
	Others	18.6%
Gonococcus		
	Shionogi	85.0%
	Cosmo Bio	15.0%
Fungus		
	Iatron	82.0%
	Cosmo Bio	18.0%
Staphylococcus		
	Eiken Chemical	60.0%
	Syntech	29.0%
	Others	11.0%
E. coli		
	Eiken Chemical	70.0%
	Denka Seiken	20.0%
	Others	10.0%
Pneumococcus		
	Shionogi	49.0%
	Syntech	34.0%
	Sumitomo Pharmaceutical	17.0%
Meningococcus		
	Sumitomo Pharmaceutical	100.0%
Influenza		
	Shionogi	64.0%
	Sumitomo Pharmaceutical	36.0%
Antiserum		
	Denka Seiken	78.6%
	Others	21.4%

Appendix 2-8) Outline of Direct Kit Market

1) Market size

(Million Yen)

	1985	1986	1987	1988	1989
Direct kit	63	258	336	473	647

2) Market size by test item

(Million Yen)

Test Item	1985	1986	1987	1988	1989
Streptococcus-A	-	170	225	340	490
Gonococcus	10	18	22	23	35
Fungus	3	4	5	8	10
Staphylococcus	6	10	15	20	25
Streptococcus-B	4	6	8	10	12
Streptococcus-C,D	40	50	60	72	75
Total	63	258	336	473	647

3) Market share by test item (%)

Test Item	1985	1986	1987	1988	1989
Streptococcus-A	-	65.9	67.0	71.9	75.7
Streptococcus-C,D	63.5	19.4	17.9	15.2	11.6
Others	36.5	14.7	15.1	12.9	12.7

4) Market share by company in 1988

Streptococcus-A	Nikken Chemicals	29.4%
	Dainabot	26.5%
	Nippon Chemiphar	23.5%
	Eiken Chemical	8.8%
	Others	11.8%
Gonococcus	Dainabot	100.0%
Fungus	Nippon Roche	100.0%
Staphylococcus	Syntech	100.0%
Streptococcus-B	Syntech	60.0%
	Sumitomo Pharmaceutical	40.0%
Streptococcus-C,D	Shionogi	100.0%

Appendix 2-9) Outline of Virus Antibody Market

1) Change of market size

(Million Yen)

	1985	1986	1987	1988	1989
Virus antibody	5,446	7,345	9,224	9,844	10,230

2) Market size by test item

(Million Yen)

Test Item	1985	1986	1987	1988	1989
AIDS antibody screen.	-	817	1,600	1,648	1,700
AIDS antibody determin.	-	10	20	28	35
ATL antibody screen.	-	815	1,618	1,996	2,100
ATL antibody determin.	-	4	20	24	50
HBs antibody	2,447	2,537	2,679	2,760	2,840
HBc antibody	480	502	504	510	515
HBe antibody	681	720	771	810	845
HA antibody	535	562	585	605	620
IgM.HBc antibody	170	190	200	200	210
IgM.HA antibody	291	306	307	308	310
HVD antibody	-	-	2	3	5
Chlamydia	1	2	3	4	5
Rubella	352	359	366	373	380
IgM.rubella	2	3	4	5	5
Herpes	19	23	25	30	35
Cytomegalovirus	34	37	40	43	45
Toxoplasma	226	234	243	251	260
RS virus	1	1	3	3	5
EB virus	16	22	24	27	30
Rotavirus	1	2	2	2	3
Influenza	20	21	21	21	22
Parainfluenza	17	18	18	18	20
Coxsackievirus	36	37	37	38	40
Poliomyelitis	9	9	10	10	12
Echovirus	21	21	21	21	22
Mumps	21	23	26	27	29
Morbilli	14	14	15	15	16
Adenovirus	14	15	16	17	18
Japanese encephalitis	2	2	2	2	2
Chickenpox	26	28	30	32	32
Others	10	11	12	13	19
Total	5,446	7,345	9,224	9,844	10,230

3) Market share by test method in 1988 (%)

Test Method / Test Item	PA	PHA	EIA	RIA	HI	HA	OTHER
AIDS antibody screening	98.8	-	1.2	-	-	-	-
ATL antibody screening	80.0	-	20.0	-	-	-	-
HBs antibody	-	72.0	7.0	21.0	-	-	-
HBc antibody	-	2.0	23.5	74.5	-	-	-
HBe antibody	-	0.8	29.6	69.6	-	-	-
HA antibody	-	-	15.0	85.0	-	-	-
Rubella	-	10.7	-	-	84.7	-	4.6
Toxoplasma	-	-	-	-	-	89.6	10.4

4) Market share by company in 1988

AIDS antibody screening (1,648 million yen)

Fuji rebio	98.8%
Others	1.2%

ATL antibody screening (1,996 million yen)

Fuji rebio	80.0%
Eisai	20.0%

HBs antibody (2,760 million yen)

Fuji Rebio	46.2%
Dainabot	25.6%
International Reagents	7.0%
Others	14.9%

HBc antibody (510 million yen)

Dainabot	74.1%
Daiichi Radioisotope	11.2%
Others	14.9%

HBe antibody (810 million yen)

Dainabot	75.0%
Daiichi Radioisotope	10.0%
Others	15.0%

HA antibody (605 million yen)

Dainabot	90.0%
Daiichi Radioisotope	5.0%
Others	5.0%

Rubella (373 million yen)

Fuji rebio	45.0%
Denka Seiken	12.0%
Dainabot	9.0%
Daiichi Pure Chemical	8.0%
Takeda Chemical	6.0%
Others	20.0%

Toxoplasma (251 million yen)

Kyowa Pharmaceutical	55.0%
Eiken Chemical	20.0%
Kainos	5.0%
Asahi Chemical	5.0%
Others	15.0%

Appendix 2-10) Outline of Virus Antigen Market

1) Change of market size

(Million Yen)

	1985	1986	1987	1988	1989
Virus antigen	4,337	4,631	4,856	5,254	5,562

2) Market size by test item

(Million Yen)

Test Item	1985	1986	1987	1988	1989
AIDS antigen	-	-	-	5	8
HBs antigen	3,514	3,709	3,800	3,875	3,920
HBe antigen	774	779	785	826	850
Rotavirus antigen	23	31	49	69	72
Chlamydia antigen	15	95	190	405	600
Herpes antigen	3	5	24	65	90
RSV antigen	-	-	-	6	10
Influenza antigen	2	2	2	2	3
Parainfluenza antigen	2	2	2	2	3
Mumps antigen	2	2	2	2	3
Morbilli antigen	2	2	2	2	3
Total	4,337	4,631	4,856	5,254	5,562

3) Market share by test method in 1988 (%)

Test Method / Test Item	EIA	RIA	RPHA	LATEX	FA	OTHER
AIDS antigen	100	-	-	-	-	-
HBs antigen	8.8	20.1	68.4	-	-	2.7
HBe antigen	30.5	68.2	1.3	-	-	-
Rotavirus antigen	17.4	-	31.9	50.7	-	-
Chlamydia antigen	64.2	-	-	-	35.8	-
Herpes antigen	-	-	-	-	100	-

Note: "FA" means fluorescent antibody method.

4) Market share by company in 1988

AIDS antigen (5 million yen)

Dainabot	100.0%

HBs antigen (3,875 million yen)

Fuji Rebio	41.0%
Dainabot	28.3%
Yamanouchi Pharmaceu.	4.8%
International Reagents	4.8%
Others	21.1%

HBe antigen (826 million yen)

Dainabot	75.8%
Daiichi Radioisotope	18.4%
Others	5.8%

Rotavirus antigen (69 million yen)

Daiichi Pure Chemical	46.4%
Nissui Pharmaceutical	26.1%
Others	27.5%

Chlamydia antigen (405 million yen)

Dainabot	64.2%
Daiichi Pure Chemical	23.5%
Others	12.3%

Herpes antigen (65 million yen)

Daiichi Pure Chemical	64.5%
Denka Seiken	35.5%

Appendix 2-11) Outline of Immunological Test Market

1) Change of market size

(Million Yen)

	1985	1986	1987	1988	1989
Infectious disease	6,450	6,780	7,092	7,343	7,730

2) Market size by test item

(Million Yen)

Test Item	1985	1986	1987	1988	1989
Syphilis	3,502	3,672	3,774	3,891	4,010
Mycoplasma	427	435	438	442	500
ASO	2,504	2,655	2,862	2,991	3,200
Widal's reaction	13	14	14	15	15
Weil-Felix reaction	4	4	4	4	5
Total	6,450	6,780	7,092	7,343	7,730

3) Market share by test method in 1988

Syphilis		
	TPHA	81.9%
	RPR card test	8.5%
	Others	9.6%
Mycoplasma		
	HA.PA	94.1%
	CF	5.9%
ASO		
	Microtitration	68.3%
	Latex agglutination	14.6%
	Others	17.1%

4) Market share by company in 1988

Syphilis (3,891 million yen)		
	Fuji Rebio	69.6%
	Kyowa Pharmaceutical	10.4%
	Sumitomo Pharmaceutical	8.2%
	Others	11.8%
Mycoplasma (442 million yen)		
	Fuji rebio	80.0%
	Kyowa Pharmaceutical	9.4%
	Others	10.6%
ASO (2,991 million yen)		
	Eiken Chemical	30.0%
	Fuji Rebio	15.0%
	Nissui Pharmaceutical	14.0%
	Kyowa Pharmaceutical	12.0%
	Others	29.0%

Appendix 2-12) Outline of STD Market

The data of the above-mentioned categories can be summarized for the STD market as follows:

1) Change of market size

(Million Yen)

	1985	1986	1987	1988	1989
STD	3,621	3,902	4,138	4,533	4,893

2) Future outlook

In most cases in the STD market, patients go directly to hospital and medical doctors tend to diagnose according to experience rather than the use of certain test. This will most likely continue in the future.

3) Market size by test item

(Million Yen)

Test Item	1985	1986	1987	1988	1989
Syphilis	3,502	3,672	3,774	3,891	4,010
Gonococcus	15	28	36	43	50
Chlamydia	16	97	193	409	605
Herpes	22	28	49	95	125
Cytomegalovirus	34	37	40	43	45
Candida	32	40	46	52	58
Total	3,621	3,902	4,138	4,533	4,893

Note: Since the size of staining and culture market is very small, it is omitted from the above table.

4) Market share by test item (%)

Test Item	1985	1986	1987	1988	1989
Syphilis	96.7	94.1	91.2	85.8	82.0
Chlamydia	0.4	2.5	4.7	9.0	12.4
Herpes	0.6	0.7	1.2	2.1	2.6
Others	2.3	2.7	2.9	3.1	3.0
Total	100	100	100	100	100

Appendix 2-13) Outline of Blood Transfusion and Transovarial Transmission (Mother to Child) Market

The data of the sections 5-3) to 5-8) can be summarized in the blood transfusion and transovarial transmission as follows:

1) Change of market size

(Million Yen)

	1985	1986	1987	1988	1989
Blood transfusion	10,113	12,319	14,402	15,398	16,078

Large market exists in tests for syphilis, HBs antigen, HBs antibody, ATLA and HIV (in order of market size).

2) Future outlook

Market for ATLA, chlamydia and herpes is expected to be growing.

3) Market size by test item

(Million Yen)

Test Item	1985	1986	1987	1988	1989
Syphilis	3,502	3,672	3,774	3,891	4,010
HBs antigen	3,514	3,709	3,800	3,875	3,920
HBs antibody	2,447	2,537	2,679	2,760	2,840
HIV (Ab, Ag)	-	827	1,620	1,681	1,743
ATL	-	819	1,638	2,020	2,150
Rubella	352	359	366	373	380
Toxoplasma	226	234	243	251	260
Cytomegalovirus	34	37	40	43	45
Herpes	22	28	49	95	125
Chlamydia	16	97	193	409	605
Total	10,113	12,319	14,402	15,398	16,078

Appendix 2-14) Outline of DNA Probe Market

1) Change of market size

(Million Yen)

	1985	1986	1987	1988	1989
DNA probe	9	43	66	78	91

2) Market size by company

(Million Yen)

Producer	Marketer	1986	1987	1988	1989
BRL and others	Cosmo Bio	30	38	48	40
Abbot	Dainabot	-	10	11	30
Amersham	Amersham Jpn	5.5	8	6.3	7
Oncogene Science	Wako Pure Chem	3.5	5	6	7
Takara Shuzo	Takara Shuzo	2	2.5	2.2	2
Biotech Research	Dia-Iatron	1.5	2	2.2	2
DuPont	Toyobo	-	-	1	1
Pharmacia LKB	Pharmacia	0.5	0.5	0.5	0.5
Total		43	66	78	91

Market Share (%)

Cosmo Bio	69.8	57.6	61.5	44.0
Dainabot	-	15.2	14.1	33.0
Amersham Japan	12.8	12.1	8.1	7.7
Wako Pure Chemical	8.1	7.6	7.7	7.7
Takara Shuzo	4.6	3.8	3.8	3.8
Dia-Iatron	3.5	3.0	2.8	2.2
Toyobo	-	-	1.3	1.1
Pharmacia	1.2	0.7	0.6	0.5
Total	100	100	100	100

Remarks:

1) All current sales are for R & D purposes only. About 60% is used for cancer research and 40% is used for basic research on biotechnology.

2) Large commercial laboratories start contract business mainly for HBV. Cosmo Bio was the first company to enter this area and their kit is now being replaced with Dainabot's product. The market share of these companies will most likely be reversed.

3) The current test method is mainly a qualitative test by the dot blotting method. The southern blotting method has to be used for a quantitative test which will require some improvement.

Appendix 2-15) Trends of Other Diagnostics Market

1) Change of Market Size (Sales Value)

(Million Yen)

Item	1986	1987	1988	1989
A. Simple Test at Hospital				
Urine test strips	8,100	8,580	8,860	9,200
Fecal occult blood (chemical)	771	705	610	557
Fecal occult blood (haemoglobin)	186	1,010	1,870	2,370
Dry chemistry reagent	195	410	840	1,130
Reagent for mini-analyzer	2,160	2,030	2,000	1,980
HCG simple test kit	215	870	1,370	1,520
Dry chemistry system	496	960	2,130	2,360
Mini analyzer	350	280	230	200
B. OTC Diagnostics out of Hospital				
Pregnancy test (self diagnosis)	570	840	980	1,150
Blood glucose test (self diagn.)	2,750	3,225	3,570	3,945
Pregnancy prediction	-	0	0	0
Urine test strips	660	750	800	850
Blood glucose self-monitoring system	443	510	578	655
C. Neonate Screening				
Phenyl-ketone	76	74	74	73
Cretinism-TSH	260	250	250	248
17-OHP	-	-	-	220
D. Mass Screening				
Workers	4,568	4,641	4,759	4,880
School student	547	547	547	546
Aged people	750	808	877	951

Note: The figures in the "mass screening" category are the values of diagnostics used for the tests.

2) **Change of Volume** (number of tests, number of examinees, etc.)

Item	Unit	1986	1987	1988	1989
A. Simple Test at Hospital					
Urine test strips	million	406	414	423	434
Fecal occult blood (chemical)	000	21,758	19,847	17,089	15,575
Fecal occult blood (haemoglobin)	000	656	4,484	8,546	10,950
Dry chemistry reagent	000	1,890	4,000	8,260	11,180
Reagent for mini-analyzer	000	20,580	19,320	19,035	18,500
HCG simple test kit	000	450	1,850	2,920	3,240
Dry chemistry system	units	415	695	1,570	1,830
Mini analyzer	units	580	540	490	470
B. OTC Diagnostics out of Hospital					
Pregnancy test	000	340	502	586	688
Blood glucose test	000	29,255	34,310	38,020	42,060
Pregnancy prediction	-	-	0	0	0
Urine test strips	million	38.7	42.9	45.7	48.5
Blood glucose self-monitoring system	units	11,570	15,450	17,500	19,850
C. Neonate Screening					
Phenyl-ketone	000 baby	1,373	1,340	1,330	1,320
Cretinism-TSH	000 baby	1,373	1,340	1,330	1,320
17-OHP	000 baby	-	-	-	1,000
D. Mass Screening					
Workers	000 man	40,800	41,500	42,500	43,850
School student	000 man	27,350	27,340	27,330	27,320
Aged people	000 man	8,133	8,800	9,500	10,310

3) Market Share by Company in 1988 (%)

Item	1988 Sales (Million Yen)	1st Rank	2nd Rank	3rd Rank	Others
A. Simple Test at Hospital					
Urine test strips	8,860	Sankyo/Ono 66.0	Eiken Chem. 14.7	Shionogi 7.5	11.8
Fecal occult blood (chemical)	610	Shionogi 68.5	Fujisawa 11.1	Sankyo/Ono 10.8	10.1
Fecal occult blood (haemoglobin)	1,870	Eiken Chem. 63.6	Fuji Rebio 19.6	Labo System 7.8	9.7
Dry chemistry reagent	840	Fuji Medical 47.6	Nagase 21.4	Sankyo/Ono 13.1	17.9
Reagent for mini-analyzer	2,089	Chugai 59.8	Amco 30.2	Dainabot 9.6	0.4
HCG simple test kit	1,370	Mochida 67.8	Dainabot 19.7	Eiken Chem. 10.9	1.6
Dry chemistry system	2,130	Fuji Medical 34.2	Nagase 33.8	Chugai 9.9	22.1
Mini analyzer	230	Chugai 43.6	Amco 30.4	Dainabot 21.7	4.3
B. OTC Diagnostics out of Hospital					
Pregnancy test (self diag.)	980	Rohto 32.6	Lion 30.6	J & Johnson 12.8	24.0
Blood glucose test	3,570	Sankyo/Ono 70.0	Kodama 7.8	Yamanouchi 7.6	14.6
Pregnancy prediction	0	Lion only			
Urine test strips	800	Shionogi 60.0	Sankyo/Ono 18.7	Yamanouchi 9.0	12.3
Blood glucose self-monitoring system	578	Sankyo/Ono 56.1	Yamanouchi 17.3	Kodama 10.0	15.7
C. Neonate Screening					
Phenyl-ketone	74	Daiichi Pure 83.8	Eiken Chem. 13.5	Fujisawa 2.7	-
Cretinism-TSH	250	Eiken Chem. 40.0	Ciba-Corning 36.0	Fuji Rebio 24.0	-
17-OHP	220 (1989)	Ciba-Corning 60.0	Eiken Chem. 39.0	Sankyo 1.0	-

Appendix 2-16) Diagnostics for Circulatory Organ Disease

1) Market size by test item

(Million Yen)

Test Item	1985	1986	1987	1988	1989
CPK	1,080	1,200	1,320	1,420	1,520
CK-MB	150	170	200	220	240
Total cholesterol	3,330	3,430	3,540	3,640	3,740
Triglyceride	2,705	2,900	3,100	3,285	3,450
HDL cholesterol	2,500	2,700	2,900	3,075	3,275
Apo/lipo-protein					
A-I/A-II	20	80	150	240	335
B	10	30	90	150	225
C-II/C-III	10	20	40	65	85
E	10	20	40	50	60
Apo/lipo sub-total	50	150	350	600	705

(2) Market share by company in 1988

CPK (1,420 million yen)

Boehringer-M-Y	28.0%
Kanto Chemical	22.0%
Wako Pure Chemical	12.0%
Eiken Chemical	10.0%
International Reagents	10.0%
Others	18.0%

CK-MB (220 million yen)

Boehringer-M-Y	27.8%
Kanto Chemical	24.2%
International Reagents	15.0%
Others	33.0%

Total cholesterol (3,640 million yen)

Wako Pure Chemical	25.0%
Eiken Chemical	20.0%
Kyowa Medex	20.0%
Nippon Shoji	10.0%
Others	25.0%

Triglyceride (3,285 million yen)

Eiken Chemical	25.0%
Wako Pure Chemical	20.0%
Kyowa Medex	15.0%
International Reagents	11.0%
Others	29.0%

HDL cholesterol (3,075 million yen)

Daiichi Pure Chemical	25.0%
Eiken Chemical	15.0%
Shino-test	12.0%
Wako pure Chemical	8.0%
Others	40.0%

Apo/lipo-protein (600 million yen)

Daiichi Pure Chemical	70.0%
Hoechst	20.0%
Others	10.0%

Appendix 3-1) Effects of Health Insurance Scores

1) Summary of Health Insurance Scores

Health insurance scores are assigned for various medical practices. One point is 10 yen and when a score of 200 points is given, 2000 yen for examination and treatment are paid.

This money is paid after applying to the Social Insurance Medical Examination Fee Payment Funds of each prefecture and an investigation.

Items are classified as evaluation fees and execution fees for clinical tests. A score is given for evaluation fees that varies with the test field and a score is given to execution fees in terms of the different methods for determination of different test items. The details of execution fees include diagnostic drugs, the technician labor, technical fees, and initial cost of determination devices.

2) Changes in Health Insurance Scores

June 1981

Full-scale re-evaluation of test scores:

Introduction of the comprehensive numerical system of rating biochemistry.

Large reduction in scores for RIA (in-vitro) tests

First health insurance score for EIA method

Comprehensive scores:

When tests of multiple items were performed simultaneously on 1 specimen, the scores were not calculated from the total score for each test item. The score was reduced by setting a maximum of, for instance, 240 points for 7 items and 520 points for 20 items or more.

Simultaneous automated chemical analysis devices became popular and countermeasures were introduced because of problems with excess tests because of handling of large amounts of specimens and simultaneous determination of 20 items.

RIA Tests:

Up to that time, only special facilities (large hospitals, etc.) had performed RIA tests and there were strict conditions attached for appropriate controls in terms of equipment.

Therefore, the initial cost burden was high. Insurance scores (very high scores) were used taking this point into consideration. However, There was a large reduction in initial cost because these tests gradually changed from special tests to general tests and it was concluded that they could be sufficiently performed with a reduction in price.

(For instance, the score for CEA tests was changed from 520 points to 350 points.)

Use of EIA:

Insulin EIA tests were first given insurance of 220 points. Insulin tests had been performed by RIA and therefore, there was a reduction in the number of tests performed by RIA. As a result, the score was reduced from 400 to 250 points.

March 1985

Second Re-evaluation of insurance scores:

Intensification of comprehensive scores for biochemistry (for example, 240 points for 5 to 7 items, 470 points for 20 items or more)

Expanded use of EIA and (correction) of score difference between RIA and EIA (10 point difference in general)

Example:
CEA (RIA) 350 points ----> dropped to 320 points
CEA (EIA) 280 points ----> dropped to 310 points

April 1986

Re-evaluation of insurance points:
RIA AND EIA became the same score

Example:
CEA (RIA) 320 points ----> dropped to 300 points
CEA (EIA) 310 points ----> dropped to 300 points

Introduction of comprehensive scores to field of immunoassay:
(thyroid items, hepatitis virus, tumor markers)

Example:
500 points for two tumor marker items became 600 points or more with cumulative system.

The actual state of tests at the time is bipolarization into in-hospital (nosocomial) tests and outside tests is proceeding. The profit with outside tests is higher than with in-hospital tests in small and medium-sized hospitals and private practices. Standardization and networking proceeded on the commercial laboratory side entrusted with the tests and cost reduction was anticipated by centralization of large quantities of specimens. Therefore, there was a dramatic reduction in money granted. Of course, price wars between rival companies is another major factor.

Consequently, there was a large difference in cost and price of tests performed on an in-hospital basis and tests performed on an outside basis.

Under these conditions, a theory was presented that there should be a different score for tests performed on an in-hospital basis and the same test performed at test centers on an outside basis. This was immediately before the introduction of so-called "one item-two prices" controls and it finally was reduced to the following form:

April 1988

Re-evaluation of insurance scores using the aforementioned argument:

Two-element system of execution fees and evaluation fees, with execution fees being re-evaluated once every two years.

The insurance score up to that point was divided into execution fees and evaluation fees and there was a drastic reduction in execution fees. One reason for this was to reduce the difference between the money granted to the test centers and the insurance score. Of course, execution fees are also used in hospitals. However, by means of this system request for evaluation fees on the hospital is seen in the sense of compensating for the reduction.

CEA RIA insurance scores are given as an example

1980 (520 points)
1981 (350 points)
1985 (320 points)
1986 (300 points)
1988 (250 points)

Actual state of comprehensive score at present time

Coagulation factor, 800 points for 3 to 4 items, 1100 points for 5 or more items

Biochemistry, 190 points for 5 to 7 items, 240 points for 8 to 9 items, 260 points for 10 to 14 items, 270 points for 15 to 19 items, 280 points for 20 items or more.

Hormones, 900 points for 3 to 5 items, 1100 points for 6 to 7 items, 1400 points for 8 items or more.

Tumor markers, 450 points for 2 items, 600 points for 3 items, 700 points for 4 items, 750 points for 5 items or more, hepatitis virus, 650 points for 3 items, 800 points for 4 items, 900 points for 5 items or more

April 1990

Approximately 2% of execution fees are reduced and the reduced value is compensated by the increase of the evaluation fees.

- Revision of comprehensive scores:

		Old Score	New Score
a. Coagulation test			no change
b. Biochemical test	5-7 tests	195	195
	8-9 tests	245	245
	10-14 tests	260	250
	15-19 tests	270	255
	over 20 tests	280	260
c. Hormone test	3-5 tests	900	800
	6-7 tests	1100	1100
	over 8 tests	1400	1300
d. Cancer markers	2 tests	450	450
	3 tests	600	600
	4 tests	700	700
	5 tests	750	(Over 5 tests)
e. Hepatitis virus	3 tests	650	600
	4 tests	800	750
	over 5 tests	900	850

- Revision of evaluation fees:

Urinalysis, fecal tests	10	15
Haematological tests	90	95
Biochemical tests	90	95
Immunological tests	90	95
Microbiological tests	90	95
Pathological tests	90	95

- Cancer screening test and malignant tumour therapeutic fee

While in case that cancer marker test (screening) is made, it has been possible to invoice the insurance score every time at the test, only once invoice is allowed now.

When a cancer is inspected by the screening, therapy by operation, radioactive treatment and drug administration is carried out. During the therapy, cancer marker is used for monitoring the progress and such monitoring expenses can first be invoiced under insurance as "malignant tumour therapeutic fee". Scores for that are 270 for general test such as RPHA and 450 for precise tests such as EIA, RIA, ELISA, LA, LPIA and PAMIA. Invoicing is allowed only once a month even if repeated tests are made for many items.

3) Future Trends in Insurance Scores

The increase in medical costs will continue to rise and exceed the increase in national income with an increase in population, an increase in the number of elderly citizens, and changes in illness structure.

Consequently, in order to control medical costs, the Ministry of Health and Welfare is planning to introduce a 10% liability per person from 1984 (20% liability in the future), and to re-evaluate examination and treatment fees and the cost of drugs. Moreover, as a rule, test scores will be reduced in the future.

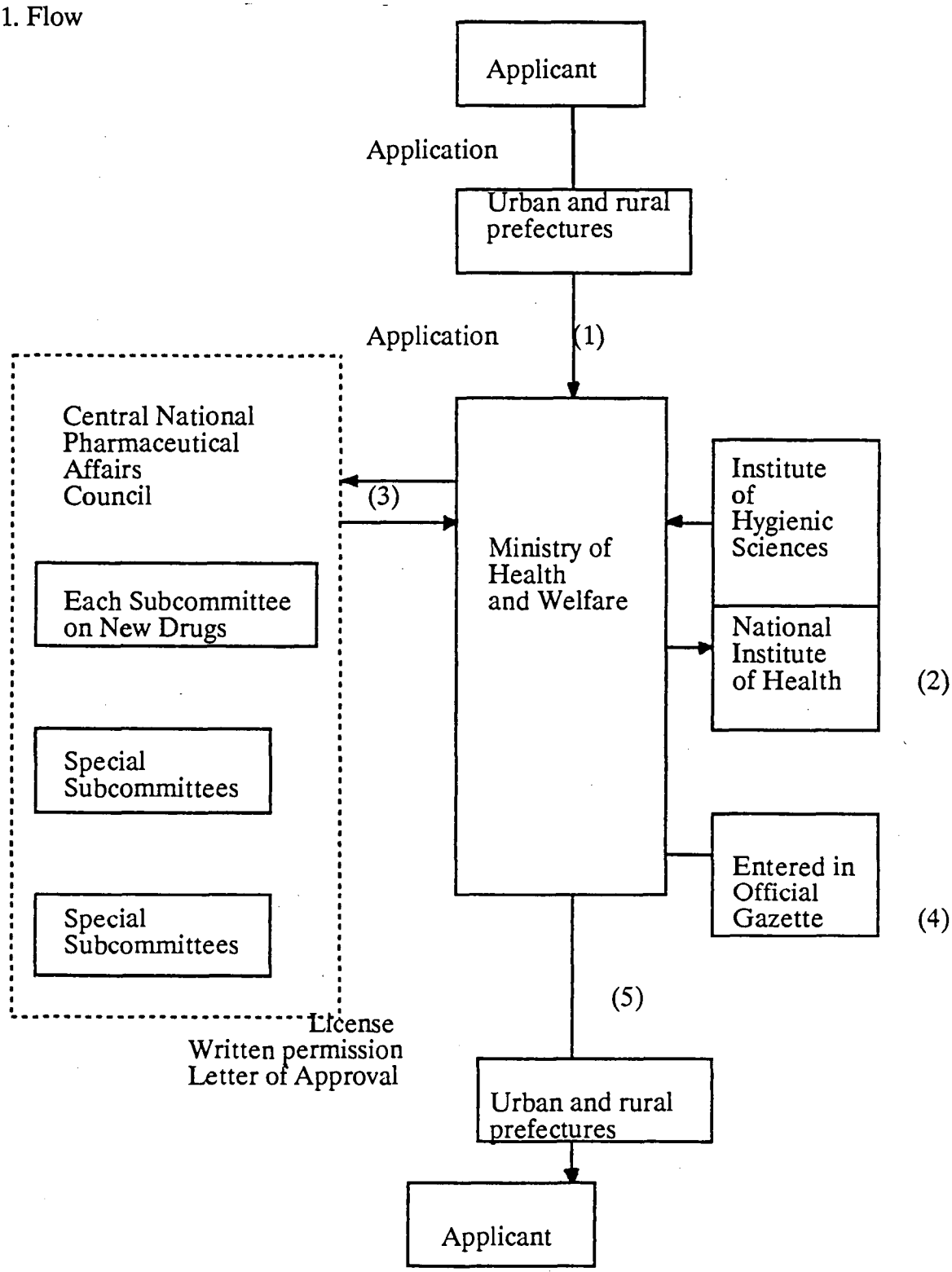
The two-element system for insurance points for evaluation fees and execution fees that was set up in April of 1988 was to reduce execution fees. Particular emphasis is placed on the fact that there is too much of a difference between the execution fees of test centers of the current insurance score.

Moreover, one idea discussed at the Ministry of Health and Welfare is a difference in insurance scores for in-hospital (nosocomial) tests, or the concept of one item, two prices.

The current insurance system of Japan involves investigation with funding, and drug costs and test costs are basically evaluated on a piece rate executed. Consequently, there is a criticism that the evaluation system always results in excessive use of drugs and abuse of laboratory test. However, in the future there is a chance that Japan will need to change to a system whereby costs ranging from diagnosis to treatment are determined for each disease as with the DRG in the U.S.

Appendix 3-2) Manufacture and Import Approval for Drugs for <u>in-vitro</u> Diagnostics

1. Flow



(2) through (4) show the course in the case of new drugs.

Furthermore, except in special cases, it usually takes 6 months from the application until permission is given. Manufacture and import are possible at this time. However, insurance does not apply and therefore, it is necessary to apply for approval to use insurance as the next step.

(However, insurance is automatically applied in division 2-2, or so-called me-too drugs.)

2. Drugs for In-vitro diagnosis (Diagnostic drugs for external use)

Handling of in-vitro diagnosis drugs was regulated as follows as drugs for in-vitro diagnostics in June of 1985.

2-1. Scope

Drugs for in-vitro diagnosis are used for diagnosis of various diseases by detection or determination of substances, etc., in specimens using samples originating from the body as the specimens and these drugs are not directly used on the body itself.

a. Purposes

1. Diagnosis of extent of body functions (functions of each organ, immune function, blood coagulation functions, etc.)
2. Diagnosis of presence of disease, site of disease, and extent of progression of disease.
3. Diagnosis of method of treatment and extent of effects of treatment
4. Diagnosis of presence of pregnancy
5. Diagnosis of blood type or cell type

b. Subjects

The following substances or items of the specimens are detected or determined:

1. Amino acids, peptides, proteins, sugars, lipids, nucleic acids, electrolytes, inorganic substances, water content, etc.
2. Hormones, enzymes, vitamins, coenzymes, etc.
3. Drugs or their metabolites, etc.
4. Antigen, antibody, etc.
5. Viruses, microorganisms, protozoa and their eggs, etc.
6. pH, acidity, etc.
7. cell and tissue or their components, etc.

c. Form

1. Drugs in the form whereby substances or items of aforementioned 2) are detected or determined by several reagents (including paper, cloth, etc., containing reagents)(so- called kits) are included. Moreover, this also includes kits from which standard reagents (for instance, standard serum) have been excluded.

2. Drugs in the form whereby the substances or items of aforementioned 2) are detected or determined by a single reagent are included.

2-2 Divisions

Drugs for in-vitro diagnosis are classified into the following divisions.

A. Division 1.

Determination items are new items (also includes cases where determination item is not new, but the determination theory is completely new).

B. Division 2.

1. Determination item is not new, but the determination method is a new method.
2. The determination items and determination methods are both conventional

Example of classification of determination method:

a. Method using agglutination reaction
b. Method using precipitation reaction
c. Method using complement fixation reaction
d. Method using hemolysis
e. Enzyme antibody method (EIA)
f. Radioimmunoassay (RIA)
g. Fluorescent immunoassay (FIA)
h. methods where the main reaction system is a chemical reaction
i. Methods where the main reaction system is a biochemical reaction (enzyme methods, etc.)
j. Physical methods (specific gravity, weight determinations, etc.)

The determination items are the same as with conventional tests, and the determination methods have been changed from qualitative methods (including semi-quantitative methods) to quantitative methods or vice versa and cases where the determination method is similar is included among "determination items and determination methods are both conventional."

2-3. Supplemental Data to be Included in Application for Approval of Manufacture or Import

This supplemental data is shown in the following table.

(Note) As a rule, the results of tests that were performed in foreign countries can be used. However, the findings of tests performed domestically must be submitted as extra data for the following cases:

1) Diagnostics for new test items
2) Diagnostics having problems with immunological reactions with substances that are detected by drugs for blood-type evaluation, and for blood coagulation factor determination, etc. with regard to clinical data or data pertaining to the correlation with previously approved products.

Supplemental Data

Remarks: 1) Data for item marked with o should be submitted.
2) Data for item marked with x should be submitted for cancer or blood transfusion related diagnostics.
3) Parentheses ( ) indicate that the applicants themselves control and manage.
4) Comments
*a Components derived from human serum
*b Components derived from human plasma
*c Simultaneous, between determiners, between determination days, between lots
*d 2 facilities or more, 150 specimens or more
*e Fifty specimens or more

Item	Division 1.		Division 2.		
Data	New determination items	New theories	New methods	Conventional	Comments
1)a. Course of development, determination methods, conditions of use in foreign countries, and significance in clinical diagnosis	o	o			
b. Course of development, determination methods, conditions of use in foreign countries			o		
c. Basic explanation of conventional items				o	
2) Materials pertaining to components of structural reagents					
a. Tests for fibrinogen	x	x	(x)	(x)	*a
b. Tests for HB virus	x	x	(x)	(x)	*b
3) Materials pertaining to kits					
a. Establishment of method of administration and dose	o	o	(o)	(o)	

Item	Division 1.		Division 2.		
Data	New determination items	New theories	New methods	Conventional	Comments
b. Properties					
Specificity test results	o	o	o	(o) Note	
Sensitivity test results	o	o	o	(o)	
Results of tests pertaining to determination scope	o	o	(o)	(o)	
Reproducibility test results	o	o	o (Simultaneous)	(o)	*c
Addition and Recovery test results	o	o	(o)	(o)	
Dilution test results	o	o	(o)	(o)	
c. Establishment of standard properties for calibration	o	o	(o)	(o)	
4) materials pertaining to establishment of storage conditions and expiration dates	o	o	(o)	(o)	
5) Materials pertaining to clinical test data	o				*d
6) Data pertaining to correlation		o	o	(o) Note	*e

Note) Data of properties (specificity, sensitivity, reducibility) and correlations of kits are needed for drugs used to evaluate blood types and drugs used for determination of blood coagulation factors, even though these are conventional items under division 2

Supplemental texts (guidelines)				
Determination methods, properties, deleterious substances	o	o	o	o
Precautions for use or handling	o	o	o	o

3. Applications for Approval for Use of Insurance

3-1. Divisions for use of insurance

The essentials of requirements desired for insurance and the divisions of use of insurance are recorded in the notes of the application for approval for manufacture and import.

Division D-1: determination items are new items
Division D-2: determination items are not new, but the determination method is new
Division D-3: determination items and methods are conventional

3-2. Dates of application for use in this case

An application for use of insurance up to the periods listed below is presented by the manufacturer (importer), etc., who has received determination of division D-1 or division D-2.

Division	Months of approval for manufacture (import)	Time limit of use of application
D-1	January to December	the 20th of the following month of each month
D-2	February to April	May 20
	May to July	August 20
	August to October	November 20
	November to January	February 20

3-3. Applications

Division D-1

1. Number of tests per reagents
2. Cost of reagents (cost per test)
3. Requested score and basis
4. Market predictions (predictions of number of patients and number of tests)
5. Summary of study (theory, determination method, comparison with other methods, properties, etc.)
6. References showing clinical usefulness
7. Other reference materials

Division D-2

1. Number of tests per reagent
2. Cost of reagent (cost per test)
3. Requested score and basis
4. Summary of study (theory, determination method, comparison with other methods, properties, etc.)
5. Clinical usefulness compared with conventional methods
6. Other reference materials

4. Determination of Treatment in Terms of Insurance and Notification of Determination

When an application for insurance is submitted, treatment of fees for examination and treatment is determined using the following divisions after investigating the details of examination and treatment:

1. In-vitro diagnostic drugs for new determination items (division D-1)
   Insurance used within 6 months after approval.
2. In-vitro diagnostic drugs for new determination method, but not new determination items (division D-2)
   Insurance introduced periodically 4 times a year.

When treatment of fees for examination and treatment is determined, applicants of use of insurance are quickly informed of the results of these determinations.

5. Inquiries into Opinions of Manufacturers and Importers

When determining how to handle fees for examination and treatment, opinions of manufacturers and importers pertaining to this application are obtained before determinations. It is important to take the time to listen to these opinions.

Once the aforementioned procedures have been completed, insurance can be applied and basic market activity of each company is developed. Consequently, it takes a period of approximately 1 year from the time of application for approval of manufacture or import.

Front

File No.

Application for Use of Insurance for in-vitro Diagnostic Drugs

Determination item

Product name

Determination purpose

Determination method

Pharmaceutical Affairs Law Approval No. and Approval Date

Insurance division

A. D-1 (new determination item)

B. D-2 (conventional determination item, new determination method)

Supervisor mailing address (telephone number)

Comments

– Use of insurance for in-vitro diagnostic drugs as applied for as described above.

Date

Address (Address of the main place of business of corporations)

Name (Name of corporation and representative) Stamp

Minister of Health and Welfare

(Back)

(For Your Reference)

Please attach the following papers to the application in accordance with the insurance division of D-1 or D-2:

(Case of insurance division D-1)

1) Number of tests per kit
2) Cost of kit (cost per test)
3) Requested score and basis
4) Market predictions (predictions of number of patients and tests)
5) Summary of study (theory, determination method, comparison with other methods, efficiency etc))
6) References showing clinical efficacy
7) Other reference materials

(Case of Insurance Division D-1)

1) Number of tests per kit
2) Cost of kit (cost per test)
3) Requested score and foundation
4) Market predictions (predictions of number of patients and tests)
5) Summary of study (theory, determination method, comparison with other methods, properties, etc))
6) Clinical efficacy compared with conventional methods
7) Other reference materials