

06/17/2014



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Proposals on the Appropriate Provision of In-vitro Diagnostics —In consideration of diversifying healthcare needs—

The Japan Association of Clinical Reagents Industries (JACRI), the IVD Committee of the American Medical Devices and Diagnostics Manufacturers' Association (AMDD), and the Medical Diagnostics Committee of the European Business Council (EBC) would like to provide the following proposals for appropriate provision of in-vitro diagnostics (IVD) for use in medical diagnostics in Japan.

Background

Clinical diagnostics are indispensable for medical practice, such as disease prevention, diagnosis, selection of treatment, and prognosis and monitoring progress in recovery. Clinical diagnostics include laboratory tests such as blood and urine specimen tests taken at medical checkups or visits to a hospital, as well as biometric tests such as ultrasound and electrocardiographic examinations. Among clinical reagents used in clinical diagnostics, clinical reagents that have been approved and licensed by the Japanese government (e.g., marketing authorization) are known as “in-vitro diagnostics” (IVDs). Use of IVDs in clinical diagnostics enables appropriate provision of highly accurate and quality-assured clinical diagnostics to the general public in Japan. Accurate test results through appropriate clinical diagnostics, for example, enable doctors to obtain data to use as the basis of

diagnosis of life-threatening diseases, such as HIV infection and Hepatitis B and C, and assist diabetic patients with their disease management by enabling them to measure their blood sugar (glucose) levels by themselves. In such ways, IVDs play an important role in maintaining health and managing disease among the general public in Japan.

With recent developments in science and technology, IVDs have started playing an important role not only in diagnosing diseases and monitoring progress as before but also aiding selection of treatments (companion diagnostics) in personalized medicine where treatments specifically customized for individual patients are provided. Furthermore, further contributions to disease prevention and maintenance of the health of the general public in Japan are expected, as it becomes possible to detect abnormalities in body before they develop into a disease and to predict the degree of risk presented by the disease.

In the report published on August 6, 2013 by the National Council on Social Security System Reform, as policy directions for reform of the healthcare and nursing care fields, the “Functional differentiation and building network” and “Health maintenance and promotion, etc.” were advocated, and the need for promotion of a community healthcare system through measures, such as incorporating local healthcare providers into networks, measures for the enhancement of home healthcare and nursing care and the maintenance and promotion of the health of the general public in Japan, and prevention, early detection, etc. of disease, was mentioned.¹ We believe that through appropriate provision and utilization of over-the-counter (OTC) reagents which can be used for Point of Care Testing (POCT: clinical testing near the site of patient care such as a patient’s bedside to obtain quick results) and self-checking purposes, we can contribute to the enhancement of home healthcare and nursing care.

We have an important role to play in appropriately providing the healthcare and medical checkup / examination facilities with clinical diagnostics related products that are useful in conducting highly accurate and efficient diagnosis, preventing disease, and maintaining and promoting health among the general public in Japan. Toward this end, we are actively addressing the many various challenges we face. Up to now, through our proposals on the handling of IVDs² and the establishment of infrastructure for companion diagnostics,³ we have engaged in extensive consultations with the Japanese government and related organizations. As a result, improvements in the IVD review and licensing system and establishment of a system for companion diagnostics have been realized, and several other

challenges are being addressed.

However, there are still many challenges remaining in healthcare in Japan today; some tests, even tests that can have a significant impact to individual's live, such as prenatal diagnosis and breast cancer risk screening, are provided to the general public in Japan without marketing authorization or clearance by the government to assure their quality, performance or accuracy. We believe that it is critical for us to build a system that enable us to provide the general public in Japan with clinical diagnostics, that can affect their health and lives, in a safe and speedy manner..

Proposal 1: Appropriate category of clinical reagents and clarification of regulatory requirements in each category by taking advancement of testing technologies and diversification of clinical needs into account.

In recent years, as progress has been made in molecular biological elucidation of disease and disease pathology, gene and protein-based biomarkers, etc. that are useful in diagnosis of diseases, disease risk determination and prediction of treatment effects/risk of side effects of drugs, have emerged, the importance of clinical diagnostics in diagnosis is increasing, and the purposes for their use are diversifying. In addition, in the cancer treatment, demand is increasing for tests that can simultaneously measure multiple biomarkers to select therapeutic drugs, and tests themselves becoming more advanced and complex, as represented by the case of genome testing that applies sequencing technology.

At present, it is necessary to clarify the clinical utility, as well as the analytic validity of a clinical reagent in order to obtain a marketing authorization as an IVD. Due to increasingly advanced and complex testing technologies and the increased diversification of clinical purpose of use, evaluations and epidemiologic studies are required for diseases with a limited target patient population to provide evidence of clinical utility, causing concerns about the risk of prolonged and increasingly large scale clinical studies. Moreover, some of newly developed clinical reagents, such as sequencing reagents used as a common reagent for multiple assays, cannot independently demonstrate their clinical utility, and they need disease specific database and an algorithm for analysis to demonstrate their clinical utility. For this reason, it takes an extremely long time for these types of clinical reagents to obtain marketing authorization as an IVD, or else obtaining of marketing authorization must be abandoned altogether, and as a result, it causes delays in provision of clinical reagents

using the latest technology to clinical medicine.

Therefore, to make the speedy and appropriate provision of clinical reagents using the latest technology to clinical medicine possible, we propose to build a system to enable their phasing introduction to clinical medicine by recategorizing clinical reagents into more appropriate categories and clarifying the regulatory requirements for each category. In other words, we believe that in a case where clinical utility remains unproven but analytic validity is recognized, it is appropriate to temporarily make the clinical reagent available to clinical medicine by granting marketing authorization as “Investigational Use Only” (IUO; as a provisional name) and subsequently grant marketing authorization and apply insurance coverage to them as “in-vitro diagnostics” (IVDs), once their clinical utility has been demonstrated. More specifically, the categories and their regulatory requirements and a comparison with the current situation are as shown below.

Current Categories

Category	Main requirements for regulatory review	Insurance coverage request by company
In-vitro diagnostics (IVDs)	Proof of analytic validity and clinical usefulness	Possible
Other than IVD (In general referred to as research reagents)	Not subject to marketing authorization review Use possible only for research purposes	Not possible

Appropriate Categories

Categories	Main requirements for regulatory review	Insurance coverage request by company
In-vitro diagnostics (IVDs)	Proof of analytic validity and clinical utility	Possible
Investigational Use Only (IUO)	Proof of analytic validity	Not possible
Other than IVDs and IUO	Not subject to marketing authorization review Use possible only for research purposes	Not possible

As the roles demanded of clinical diagnostics continue to diversify, we propose the adoption of a new system that enables their more flexible and appropriate use in clinical medicine.

Proposal 2: Establishment of a system relating to clinical research with the aim toward the promotion and acceleration of IVD development.

In order to manufacture, import and sell IVDs, it is necessary to undergo a review, as required by Pharmaceutical Affairs Law (Pharmaceutical and Medical Device Law), and shortening the period required for both development and review is an important task to enable the early provision of new IVDs to clinical medicine. In recent years various measures for improvements have been made to reduce the review period, such as the “Plan for Collaboration to Accelerate IVD Evaluation (Fiscal Year 2014 to 2018)”⁴ formulated by the Ministry of Health, Labour and Welfare. Further significant reductions in the review period can be expected if the review process is further streamlined under the “Least Burdensome Approach.”

Meanwhile, other remaining challenges include the reduction of the development period for new IVDs. In IVD development, it is necessary to conduct clinical performance testing on numerous clinical specimens, including specimens from patients and healthy subjects, to prove clinical utility of the IVD. However, ethical and other guidelines relating to conducting clinical research have become stricter in recent years, and companies who develop clinical reagents are required to invest considerable time and financial resources to conduct clinical performance studies. Furthermore, since no guidelines have been established on clinical performance studies for IVDs, there are no clear rules to protect the human rights of subjects participating in the studies or to ensure appropriate study design, and there is also an issue that the system for accepting clinical performance study varies among medical institutions. This situation causes prolonged development periods and becomes an obstacle to IVD development itself. Therefore, we believe that the establishment of clinical performance study guidelines that take the characteristics of IVDs into account is essential for the appropriate and speedy implementation of clinical performance testing.

Moreover, we also believe that, since it is possible to use residual specimen or saved

specimen to evaluate the performance of IVDs, the establishment of a specimen bank, in which specimen from patients and healthy subjects could be collected and saved in advance for use when needed, would be effective in reducing IVD development periods. By utilizing a specimen bank that stores appropriately collected, in compliance with ethical and other guidelines, residual specimens from clinical diagnostic tests conducted in regular medical check-ups and medical examinations, it would be possible for us to use the valuable clinical specimens efficiently and thoroughly in the development of advanced IVDs. Specimen banks have already been launched in some medical institutions, but since the types of diseases and the number of specimens, etc. are limited, and methodologies for use of specimen banks have not been established, in reality, they have not been used in IVD development. We strongly desire the establishment of a specimen bank in which patient specimens encompassing various diseases and specimens from healthy persons of a wide range of ages are appropriately collected and stored for use in the development of IVDs, as well as the establishment of rules for its use, to enable earlier provision of IVDs using the latest technologies to clinical medicine.

Proposal 3: Promotion of use of IVDs in home healthcare, nursing care, community healthcare, and self-care.

(1) Promotion of use of POCT in home healthcare, nursing care and community healthcare

In recent years, use of POCT (Point of Care Testing: on-the-spot tests in clinical medicine/bedside testing) has drawn attentions as clinical diagnostics that can be implemented outside of the laboratory in clinical medicine. POCT can contribute to the provision of high quality healthcare based on a quick diagnosis and treatment, since highly accurate results can be obtained as necessary by performing testing while at the side of the patient. POCT makes it possible for testing to be provided at the site of various medical service provision, without being limited to medical institutions alone, and in particular, we expect that through active use of POCT during home visits, at visiting nursing stations, and on similar occasions, it can become an essential tool for the promotion of community healthcare, enabling the transition from in-hospital to home healthcare.

As described previously, making POCT widely available is desirable, but there are several challenges that need to be addressed in order to realize it. Firstly, the quality of

tests must be secured. While POCT enables us to obtain results conveniently, routine accuracy management, maintenance of devices, etc., and expert knowledge and skills relating to the operation and interpretation of measurement results are required for highly accurate and appropriate test report. We believe that it is essential to designate POCT specific coordinators and develop human resource for the appropriate provision of POCT.

The second challenge is to realize appropriate insurance reimbursement coverage for POCT. Based on the need in clinical medicine to perform convenient and appropriate testing at a patient's side, various technological developments are in progress to make POCT devices smaller and to improve operation. We strongly desire the introduction of a new insurance reimbursement scheme for promoting and making POCT widely available to realize the patient side testing, a separate system from the reimbursement system for the tests conducted in laboratories at medical institutions.

By promoting availability of POCT needed for developing community healthcare and enhancing home nursing and healthcare, and building a collaborative system where necessary tests can be performed not only by physicians but also by nurses, pharmacists, medical technicians, public healthcare workers, etc. and appropriate information can be provided to a physician, we will continue to develop this field as one that is useful for community healthcare and healthcare collaborations.

(2) Promotion of use of IVDs in Self-care

Awareness on Self-care, take care of one's health oneself, is growing, due to rising healthcare costs caused by aging society and the increase in psychological illness and age-related, lifestyle-related, or social-environment-related illnesses. In this context, self-checks, whereby people review their health status themselves, are also increasingly attracting attention from the perspective of preventive medicine, such as personal health management and early detection and diagnosis of diseases. However, the current environment is not sufficient for conducting self-checks, and we believe it is important to establish a system and regime utilizing IVDs for enabling the provision of appropriate self-checks.

(i) Provision of appropriate testing in clinical test facilities

Under the Ministry of Health, Labour and Welfare Notification of March 31, 2014, the legal status of clinical test facilities has been established,⁵ and it has become possible for

pharmacists and other healthcare providers to perform simple test procedures, such as obtaining blood specimen from fingertip with a lancet. Testing at clinical test facilities such as pharmacies will create further opportunities of self-checks for the population who previously lacked opportunities to undergo medical checkups, including people who are not employed, such as young people, housewives, and the elderly. Also it is considered that self-checks can be effective in early detection and prevention of lifestyle-related illnesses, etc. through collaboration with community healthcare institutions, etc. On the other hand, as is shown in the Guidelines on Clinical Test Facilities,⁶ their safe and appropriate operation is also important, and we believe the following challenges exist relating to the appropriate conduct and making testing available at clinical test facilities.

- Improve availability of POCT compatible reagents and instruments whose maintenance and accuracy management are simple to perform and require small amount of blood from a finger-prick for measurement.
- Build an infrastructure to provide appropriate tests with sufficient accuracy and precision at clinical test facilities, including systems for the maintenance and accuracy management of testing instruments and reagents. In other words, a system should be built to provide systematic education and training on specialist knowledge and skills, such as methodologies for measurement and accuracy management, to pharmacists and other healthcare professionals responsible for testing.

In order to provide correct test results at clinical testing facilities which would become more popular in coming years, we believe that a system should be established, as a matter of urgency, to provide appropriate tests at clinical test facilities by addressing challenges in both operation and infrastructure aspects.

(ii) Appropriate use of over-the-counter (OTC) reagents

The scope of OTC reagents that can be used for self-checks has not increased in over 20 years since the tests for glycosuria, proteinuria, and pregnancy were approved as OTC reagents in 1990 and 1991. One of the reasons why OTC reagent tests have not become widely available is that rules for switching professional-use IVDs to OTC reagents have not been established. However, in response to the proposal from the Cabinet Office's Council for Regulatory Reform, which supports building a system and rules at the earliest opportunity, measures have now been launched aiming at a system to be operational during fiscal 2014,

and it is highly likely to promote the approval of professional-use clinical reagents as OTC reagents

One remaining issue to be addressed in near future is to expand the scope of test items for which OTC reagents can be used. Regarding this question, in “Basic Thinking on Introduction to the Field of Self-care” (First phase report by the Year 1990 Study Group), the conditions for use of OTC reagents were given that OTC reagents can only be used for qualitative and semi-quantitative tests which can be performed with specimens obtained in a non-invasive manner. Tests meeting these conditions include tests for fecal occult blood, ovulation period, urine occult blood, and influenza. However, technological advancement in recent years has made possible safe blood specimen collection by using a lancet on fingertips and easy-to-use medical devices have been developed, we believe that the quantitative tests using combination of the blood specimen collected with a lancet in a low-invasive way and easy-to-use medical devices should be considered as a candidate test item for the use of OTC reagents, in addition to the tests recognized in 1990. OTC reagents should be used not only for the purpose of diagnosis of diseases but also for encouraging people to consult a medical institution if an anomaly was found. Or else they should be used under regular health management for lifestyle-related illnesses which often lack subjective symptoms. For this reason, we believe that tests which is useful for self-checks to review one’s own health status oneself, such as blood glucose, HbA1c, lipid tests for cholesterol, etc., and hepatic function tests, should be considered as candidate tests for which OTC reagents should be available.

In order to widely utilize OTC reagents that would benefit preventive medicine, such as health management and early detection and diagnosis of diseases by the general public in Japan, establishing a system that accommodate broad range of OTC reagents and education for promoting appropriate use of self-checks is urgently needed.

End.

Reference Materials

- 1) Report of the National Council on Social Security System Reform (Overview): Path to leaving assured social security for future generations (National Council on Social Security System Reform, Aug. 6, 2013)

<http://www.kantei.go.jp/jp/singi/kokuminkaigi/pdf/houkokusyo.pdf>

- 2) Opinions on the Handling of IVDs
(JACRI, AMDD, and EBC, Aug. 4, 2010)
<http://www.jacr.or.jp/osirase/shiryoudoc/100804IVDPositionPaper.pdf>
- 3) Proposals on the Establishment of Infrastructure for Companion Diagnostics for Promotion of Individualized Healthcare (JACRI, AMDD, and EBC, Oct. 21, 2011)
<http://www.jacr.or.jp/osirase/shiryoudoc/111021teiansyo.pdf>
- 4) Plan for Collaboration to Accelerate IVD Evaluation (Fiscal 2014 to 2018)
(Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, Mar. 31, 2014)
<http://www.mhlw.go.jp/file/04-Houdouhappyou-11124500-Iyakushokuhinkyoku-Iryoukikishinsakanrishitsu/taishin.pdf>
- 5) Notification on Partial Revision of Facilities Prescribed by the Minister of Health, Labour and Welfare Based on the Provision of Article 20-3, Paragraph 1 of the Act on Clinical Laboratory Technicians, etc. (2014 Ministry of Health, Labour and Welfare Notification No. 156)
<http://www.hourei.mhlw.go.jp/hourei/doc/hourei/H140401G0350.pdf>
- 6) Guidelines on Clinical Test Facilities (Health Policy Bureau, Ministry of Health, Labour and Welfare, Apr. 9, 2014)
<http://www.hourei.mhlw.go.jp/hourei/doc/tsuchi/T140411G0070.pdf>

- Japan Association of Clinical Reagents Industries (JACRI)

Japan Association of Clinical Reagents Industries is an organization composed of companies that contribute to the medical care and welfare of the people of Japan by manufacturing (or importing) IVDs for sale to medical institutions in Japan, mainly through pharmaceutical wholesalers, as well as export of IVDs to the world market at large. The purpose of the Association is to pursue the original mission of IVDs and ensure compliance with related laws and regulations, as well as to develop and spread high quality and performance products through the development and introduction of advanced technology, with response to the demands of the people of Japan as its weighty responsibility. The Association aims for the healthy development of the industry by further enhancing its business performance capabilities and organizational foundations as an industry organization for clinical reagents. See www.jacr.or.jp for details.

- American Medical Devices and Diagnostics Manufacturers' Association (AMDD)

The American Medical Devices and Diagnostics Manufacturers' Association (AMDD) was established on April 1, 2009, and is an industrial organization composed of 67 Japanese arms of US companies (as of end March 2012) mainly providing advanced medical technologies, such as medical devices and IVDs. AMDD member companies provide a broad range of advanced medical technologies, from coronary pace-makers and ICD, cardiac valve prostheses, catheters such as PCI, stent grafts, surgical apparatus and instruments including prosthetics, intraocular lenses, large diagnostic imaging devices, genetic diagnosis, IVDs and system devices. Member companies create a total of approx. 21,000 or more jobs in Japan and are involved in various activities to contribute to the improvement of healthcare in Japan through the provision of advanced medical technologies. See <http://www.amdd.jp> for details.

- European Business Council (EBC)

The European Business Council (EBC) is an organization in charge of trade policy for the 17 countries of the European Chamber of Commerce and Business Associations in Japan. Since its establishment in 1972, the EBC has been working to improve the trade and investment environment for European companies located in Japan. At present, we represent over 2500 corporate and individual members who belong to the European Chamber of Commerce. Of these, approx. 300 companies participate in the EBC's 29 industrial committees and are involved in wide-ranging work in their respective economic

fields. The EBC seeks to closely collaborate with the EC Mission to Japan, the Embassies of member countries and other European business associations in Japan, while making proposals and recommendations to the Japanese government for the establishment of an open trade and investment environment. See www.ebc-jp.com for details.