

Strategy of SAKIGAKE

～Leading the world in the practical application of innovative medical products and devices～

17 June, 2014

SAKIGAKE PT

Ministry Project Team to lead the world in the practical application of innovative medical products

Strategy of SAKIGAKE

Ministry Project Team to lead the world in the practical application of innovative medical products

June 17, 2014

I. Introduction

- The ‘Japan Revitalization Strategy’ and the ‘Healthcare and Medical Strategy’ were adopted on June 14, 2013, declaring that the Government of Japan (GOJ) would promote the practical application of pharmaceuticals, medical devices, and regenerative medicines that are the core of medical excellence, and that GOJ would create cutting-edge, innovative medical products with the potential to acquire a share of the expanding global market. Based on this, the bill of “Act to Promote Healthcare and Medical Strategies” was submitted to the current Diet session and enacted on May 23, 2014.

- In line with these actions, the Ministry of Health, Labour and Welfare (MHLW) has discussed policies to promote the development of pharmaceuticals, medical devices and regenerative medicines. The MHLW introduced the “Vision for the Pharmaceutical Industry 2013” and “Vision for the Medical Device Industry 2013” on June 26, 2013, which depicted visions for the medium and long terms aiming at having pharmaceutical and medical device industries play a major role in creating innovation with international competitiveness. In addition, the revised Pharmaceutical Affairs Act and legislation to ensure the safety of regenerative medicine were also enacted during the Diet session in November 2013 to encourage development and enhance the safety measures of innovative medical products and to provide regenerative medicine promptly and safely, respectively.

- In this context, the MHLW assigned Minister’s Secretariat to serve as chief of the Ministerial Project Team (SAKIGAKE PT) that will aim to pioneer the practical application of innovative medical products, in December 2013. It also decided to plan strategies as a package covering from basic research to clinical research/trials, approval reviews, safety measures, insurance coverage, improvement of infrastructure and the environment for corporate activities, and global expansion.

As the first step, the SAKIGAKE PT discussed mainly the pharmaceutical product field with related divisions within the MHLW and examined pertinent policies, by interviewing the

experts from industries and academia. The Strategy of SAKIGAKE can be characterized as the embodiment of “Vision for the Pharmaceutical Industry 2013”, as well as action plans to implement Healthcare and Medical Strategies.

Activities that are applied to not only pharmaceutical products, but also medical devices and regenerative medicines, were specified as such. The strategy of SAKIGAKE covers policies specifically related to medical devices and regenerative medicine that were individually examined by SAKIGAKE PT were also included.

- Japan is well recognized for its strength in basic research, which has allowed Japanese academia to produce many promising seeds. However, it has also been pointed out that the weakness lies in finding practical application for these seeds for many years. Producing innovative pharmaceutical products ahead of other countries requires a development plan and strategies with a conscious of unmet medical needs from the research stage. Government support for the series of development steps from basic research through global expansion, for instance facilitation of streamlined research and development, is also important to nurture seeds into “first in class” innovative medical products. To date, while leading pharmaceutical companies in Japan have expanded their overseas presence, a majority of Japanese companies have developed their strategies suitable only for the Japanese market. Behind the trend is the fact that many Japanese companies have been developed their marketing strategies based on the National Health Insurance (NHI) drug price scheme. They are now facing challenges such as the growing presence of foreign products and expansion of share of generic drugs, as well as limitations due to the nature of the public market. Going forward, it will be essential to develop global marketing strategies to export innovative pharmaceutical products meeting the needs in export markets. That in turn will demand that clear objectives be set, without fear of failure, for the development and market expansion of innovative pharmaceutical products.
- When focusing on the development of innovative medical products, efforts to further enhance safety measures for medical products should become increasingly important. It is important to establish an environment that can facilitate the development and global market expansion of innovative medical products by achieving qualitative improvements in safety measures based on risk-benefit evaluation methods over the entire period from the development stage and approval review to post-marketing, as well as providing information to overseas markets.
- Recognizing these issues, the Strategy of SAKIGAKE consists of the “SAKIGAKE Designation System” and the “scheme for rapid authorization of unapproved drugs”. The former promotes R&D in Japan aiming at early practical application for innovative

pharmaceutical products, medical devices, and regenerative medicines. The latter accelerates the practical application of unapproved/off-label use of drugs for serious and life-threatening diseases by expanding the scope of the Council on Unapproved Drugs/Off-label Use to include unapproved in Western countries if it satisfies certain conditions and by improving the environment for companies to undertake development of such drugs. The Strategy of SAKIGAKE will describe the specific policies that the MHLW should address in the future, for each item including the promotion of research and development, strengthening of review systems and safety measures, drug pricing system, improvement of the infrastructure and environment for corporate activities, and global expansion. It will then show examples of support measures as a package for innovative medical products.

- The MHLW will implement these policies during the budgetary request process in FY2015, but some of them which are ready will be executed in 2014 ahead of schedule.

- Serious misconduct in several clinical trials came to light in the past year. Reliability of Japan clinical studies is now being questioned. The MHLW is currently discussing measures including legal action in light of the findings by the investigative committee for the clinical studies of antihypertensive drugs. As a result, the principle of clinical research in Japan should be revisited in terms of the quality of clinical research, patient protection, transparency, and management of conflicts of interest, considering the results from clinical research could lead to the creation of innovative medical products rapidly. The system that supports first-in-human clinical research should also be established.

II. Specific Policies the MHLW Should Address

1. Promotion of Research and Development

(1) Promotion of stronger research and development of medical products through Health and Labour Sciences Research Grants as well as the coalition between the Pharmaceuticals and Medical Devices Agency (PMDA) and the Network for Drug Discovery

- To further promote practical application for prominent seeds that have been discovered in academia etc., Pharmaceutical Affairs Consultation on Research and Development Strategies by PMDA and utilization of the Network for Innovative Drug Discovery and Development should be bolstered for researchers. Specifically, for the researches focusing on practical application of the seeds, the system to adopt the research theme appropriately reflecting the results from the regulatory consultation on research and development strategy by PMDA in selecting the research theme funded by Health and Labour Sciences Research Grants, will be considered in cooperation with the Japan Agency for Medical Research and Development. In addition, it aims to be a one-stop service through joint on-site individual consultation by PMDA and the Center for Innovative Drug Discovery and Development at major society meetings and other follow up services.
- Support through Health and Labour Sciences Research Grants for the development of medical products that private companies are less motivated to research and develop, such as drugs for pediatric cancer, sarcoma, and rare diseases, will be strengthened so that those can be studied in an industry-sponsored clinical trials.
- Since a multidisciplinary treatment that adequately combines surgery, radiotherapy, pharmacotherapy and immunotherapy has the best therapeutic effect for the treatment of cancer, support by Health and Labour Sciences Research Grants allocated for multi-center clinical trials in order to develop not only drugs but also optimal treatment regimens or combinations should be intensified. Moreover, infrastructure to conduct clinical trials such as promoting disposition of clinical research coordinators (CRC) at Designated Cancer Care Hospitals will be established.
- In cancer research, “the research on development of novel drugs fulfilling unmet medical needs” and “the research on creating new standard of care” will be enhanced, according to the newly formulated “Comprehensive Ten-Year Strategy for Cancer Control.”

- The bill of “Act on development of related laws to enhance integrated services for healthcare and nursing care in community” was submitted during the current ordinary Diet session in order to help patients return home or work early and live in a familiar community. Aligned with this, a research for practical application of home medical equipment based on a survey of needs in home care practice will be supported.

(2) Promotion of drug repositioning (DR), such as development of off-label use for existing drugs including off-patent drugs

- The research and development of orphan drugs etc., will be promoted by reallocation of the grants for evidence collection of DR research mainly done by the universities.
- The measures to promote development activities for additional indications or drug repositioning to the local drugs need to be considered: For example, the drugs used widely in Japan or requested for development by healthcare professionals are to be presented to the scheme of the Council on Unapproved Drugs/Off-label Use (e.g. prioritize a review of drugs for specific diseases in Japan or East Asia).

(3) Promotion of regulatory science (RS) to guide practical application of cutting-edge technologies for researchers, pharmaceutical companies and venture enterprises developing regenerative medicine

- People and patients always have a need for innovative medical products and devices. To promptly provide them to healthcare professionals, the quality, efficacy and safety must be ensured through scientific prediction evaluation and judgment as well as from the ethical viewpoint of whether it is appropriate for the patients. Promotion of regulatory science (RS) for that purpose is increasingly important. It shall clearly show the process of practical application for cutting-edge technologies and help streamline research and development, reduce costs, and improve the success rate. It is therefore necessary for PMDA to promote research into the establishment of quick and accurate evaluation methods based on the latest scientific technologies in collaboration with research and medical institutions such as universities and the National Institute of Health Sciences (NIHS).

(Note) Regulatory science (RS): “RS is a science that provides appropriate predictions, evaluations, and judgments to incorporate the outcomes of technology into the most desirable form for people and society.” (Basic Program for Science and Technology [approved by the Cabinet on August 19,

2011]) Promotion of these visions is stated in the Act to Promote Healthcare and Medical Strategy.

(Reference) Article 13, paragraph 2 of the Act to Promote Healthcare and Medical Strategy

In applying for the outcome from the medical research and development pragmatically, the Government shall take necessary measures to develop adequate systems, secure human resources and improve the technology for the promotion of science so as to make appropriate and prompt prediction, evaluation and judgment based on the quality, efficacy and safety of products.

- Specifically promoting the research into evaluation methods for adverse effects (off-target effect: binding to non-target sites) of the cross-linked artificial nucleic acid that Japan has pioneered and that is expected to have an advantage in terms of manufacturing costs given its shorter base length or the research into the establishment of disease-specific biomarkers (including genetic markers) and clinical performance tests of companion diagnostics towards the realization of personalized medicine, as well as the development of new official test methods as a basis for the development of drugs (the official method for evaluating the quality of the drug in the Pharmacopeia of Japan such as the quality test methods for nanotechnology-derived drugs or new safety test methods for alternative test methods) and RS research on streamlining clinical and non-clinical trials such as biokinetics.

- Development of human resources with a thorough knowledge of the RS research through personnel exchanges between universities having conducted the latest research and PMDA/NIHS should be enhanced, while guidelines to develop and evaluate innovative pharmaceutical products, devices, and regenerative medicines with promising practical application, will be also prepared, utilizing the results from RS research, with the concerted efforts of researchers and PMDA reviewers.

(Major cases of research)

- Guidelines for cancer vaccine, nucleic acid medicine, pediatric diseases, gene-therapy drugs, drugs for Alzheimer's disease, personalized medicine, molecular imaging
- Guidelines for medical devices including next-generation ventricular assist devices, minimally invasive therapeutic instruments, orthopedics and dentistry, and stent durability test
- Guidelines for individual regenerative medicines that are used for the treatment of cerebral infarction and spinal cord injuries or that are derived from ES/iPS cells, as well as cardiomyocyte and corneal sheets, cartilage, and platelets.

(4) Research and development through public-private joint project

- Issues to remove bottlenecks in the development of drugs originated in Japan will be identified, and an ‘research and development partnerships’ will be formed for each issue in which interested parties, such as academia, the pharmaceutical industry, the National Center for Advanced Medical Technology and so on, can perform an intensive research.
- The NIHS and pharmaceutical industry will jointly perform quality risk evaluation of antibody drugs, aiming at accelerating the development of innovative antibody drugs and promoting research on establishing methods for manufacturing quality control.
- The screening center of the National Institute of Biomedical Innovation (NIBIO) shall play a central role in establishing a coordination system by industry-academic-government researchers who have studied antibody drugs and nucleic acid medicine across the nation to promote all-Japan development of antibody drugs and nucleic acid medicine.
- The NIHS and pharmaceutical industry will jointly collect and analyze biological samples (such as blood and urine) focusing on serious adverse effects (such as interstitial pneumonia) considered to be prevalent in Japan as compared with Western countries, and develop biomarkers (including genetic biomarkers) that can be used in early and advance diagnosis of adverse effects, and construct a bank of biological samples for provision to external parties in cooperation with the National Institute of Biomedical Innovation.

(5) Development of safety evaluation test methods for cardiotoxic drugs by using cardiomyocyte derived from iPS cells

- Test methods to evaluate the safety of drugs without administration to humans can be anticipated using cardiomyocyte differentiated from human iPS cells.

To this end, the next-generation test methods for cardiotoxicity using new technologies for human iPS cells, an area in which Japan excels, will be sought to develop standard cells for evaluating the mature ventricular muscle type that can detect not only QT prolongation but also arrhythmogenic effects, which commercial cells cannot detect. In addition, research into the development of standard test methods using these cells shall be conducted by all-Japan industry-academic-government organizations to promote commercialization of, and international standardization of the evaluation methods for these cells.

Furthermore, research shall be conducted into standard test methods using synapse formation by human iPS cell-derived nerve cells and physiological changes in neural function-maturation as indices, as well as research into evaluation methods for drug-metabolizing enzyme induction using human iPS cell-derived liver parenchymal cells.

(6) Implementation for high-quality clinical research and activation of clinical trials in Japan

- Clinical trial core hospitals as well as the clinical trial centers for early/exploratory clinical studies which are on-going government-funded projects shall play a pivotal role in conduct of high-quality clinical research in Japan. Clinical trial core hospitals are positioned under the Medical Care Act as the central research hospitals with an Academic Research Organization (ARO) function to support the planning and execution of clinical research for other institutions.

This shall produce the following effects:

- 1) Clinical trial core hospitals support other medical organizations in conducting clinical research. In collaborative research, clinical trial core hospitals play a central role to improve the quality of clinical research conducted at other medical organizations,
- 2) Patients who are willing to participate in clinical research can access these hospitals based on knowledge of hospitals conducting high-quality clinical research,
- 3) Collection of data under the well-controlled system shall streamline clinical research,

These are expected to promote high-quality clinical research for the development of innovative medical products.

- At these clinical trial core hospitals, the following measures shall be taken to facilitate research on practical application for innovative pharmaceutical products and devices.

- Prioritized allocation of grants

At these core hospitals, collaboration with the centers for translational research of the Ministry of Education, Culture, Sports, Science and Technology (MEXT) is strengthened to establish a system for consistent management from basic research to practical application. Given projected increases in the number of seeds for practical application, allocation of grants is prioritized to further promote research.

- Use of research data

The data from the clinical research conducted in the clinical trial core hospitals, which are taken in accordance with ICH-GCP, enable an efficient application for regulatory approval to supplement the data for clinical trials.

- Promotion of clinical research and trials

Clinical trial core hospitals are assumed to have extensive experience in multi-center clinical research, international clinical research, investigator-initiated clinical trials, and first-in-human studies. It is also assumed that a greater number of clinical trials are conducted at these hospitals than at other medical institutions. Therefore, the on-site GCP

inspection shall be performed in a reasonable way, so as to reduce the workload checking reliability of clinical trials conduct.

- Promotion of advanced medical care

Clinical trial core hospitals shall be exempted from several cases of actual clinical experience which are required as prerequisite in applications for advanced medical care.

- Conduct of research in cooperation with the intractable disease study group

Research on rare diseases without known treatments to date through active cooperation with the intractable disease study group should be enhanced. Also, ways to reduce necessary workload such as utility of the research data for post-marketing safety measures shall be considered.

- Further promotion of high-quality clinical research and investigator-initiated clinical trials at the National Center for Advanced Medical Technology are encouraged to make the data used for regulatory approval.

(7) Support for orphan drugs research and development

- The environment for the development of orphan drugs for the treatment of diseases with very few patients (i.e. ultra-orphan drugs, devices, and regenerative medicines) should be improved by clarifying the designation criteria and accelerating early designation. In addition, further support measures including rational designation and evaluation methods aiming at expanding support for research and development and achieving early practical application for these drugs ahead of the other countries shall be considered.
- The intractable and rare disease study groups shall use the new system of patient registry and proactively contribute to post-marketing safety measures by pharmaceutical companies to promote the use of clinical research data in their post-marketing surveys.

(8) Strengthening the consultation system by PMDA

- Pharmaceutical Affairs Consultation on Research and Development Strategies will be enhanced so as to eliminate time lags in drug development by providing advice for development processes (roadmap), planning a study protocol of confirmatory studies, and development strategy for pharmaceutical companies.
- As for the pre-application consultation, the Pharmaceutical Affairs Consultation on Research

and Development Strategy, and the simplified consultation, the consultation on clinical trials will be enriched by adding new consultation framework as an option, based on the applicant's needs including reliability standards, via exchange of opinions with interested industries or analysis of consultation items.

- Cooperation with overseas regulatory agencies in information sharing will be enhanced to increase the ratio of multi-regional clinical trials in which Japan participates by 2018, leading to resolve the time lag in drug development.
- Guidelines for the reviewers and the consultation system will be expanded, to contribute to the development of orphan drugs.

(9) Support for drug development and safety measures through Medical ICT

- Technologies to view and extract the necessary information electronically from electronic medical records etc., will be developed, introduced, and standardized, in order to streamline and accelerate clinical research/clinical trials and to maintain the quality of information. Specifically, 1) introduction of a system to develop case reports by linking the hospital information system and electric data capturing (EDC), 2) conversion of clinical trial-related documents into electric form, and 3) implementation of remote SDV (Remote Source Document Verification: reading, investigating, and verifying raw data of clinical trial data through such as telecommunication lines) for efficient monitoring will be done.
- A database for the medical information will be expanded in terms of both quality and quantity of data. Also, the environment for its utilization, such as development of the risk-benefit evaluation method for drugs with the accumulated data or planning of safety measures and related areas, will be improved. This may enable to analyze the information that is currently difficult to estimate, for example, adverse effects with low incidence rate or an adverse effect for each concomitant drug, and also can be reference for safety measures for future drugs.

(10) Scheme for rapid authorization of unapproved drugs

- The scope of evaluation by the Council on Unapproved Drugs/Off-Label Use will be expanded to include drugs unapproved in Western countries if it satisfies certain conditions, and requesting companies to develop such drugs to accelerate practical application for the treatment of serious and lethal diseases. In addition, collecting data in investigator-initiated clinical trials conducted at the clinical trial core hospitals and the National Center for Advanced Medical Technology will be encouraged to support for research and development and to

improve the development environment, especially for the unapproved drugs in Western countries, considering it will take time for matching between a product and a company who will be able to develop it in Japan.

(11) Strengthening the development system for vaccines

- The Immunization and Vaccine Sub-Committee of the Health Science Council selected vaccines with high priority for development that are necessary for infection control measures based on medical needs and designated them in the immunization basic plans. Research and development, and practical application for these vaccines developed in Japan or with new technologies or improvement will be promoted by supporting research and development and reviewing periodically the development status.

2. Strengthening the structure of PMDA for Review and Safety Measures

(1) Strengthening the structure and improving the quality of PMDA review and safety measures

- Improving the quality of reviews and shortening the lag in review period will be achieved by accelerating the review process considering the characteristics of pharmaceutical products, devices, and regenerative medicines. For this purpose, the structural buildup necessary for further enhancement of safety measures will be done, using own financial resource as well. The maximum number of full-time employees is set to be 1065 in the end of the third mid-term target.
- Strategic human resource development, to hire advanced and specialized staff will be considered, for instance, increasing the number of limited-term employees or introducing an annual salary system.
- The structure of PMDA will be organized to introduce the electronic submission of the clinical trial data for new drugs should be accepted by the PMDA for the application for approval submitted from 2016. Moreover, the PMDA will conduct their own research and analysis with modeling and simulation (MS) using clinical trial data and provide advice to improve the quality of review and consultation. In addition, the PMDA shall also develop guidelines, aiming to contribute to further increase in the quality of review and consultation, and perform cross-cutting analysis by using advanced analytic and predictive evaluation methods such as MS to streamline the drug development process.
- New methods for compliance inspection (e.g. CDISC: Clinical Data Interchange Standards

Consortium) to ensure the reliability of data submitted in the application for approval need to be introduced.

- Onsite training at medical institutions or corporate manufacturing sites will be implemented. In addition, the qualification and ability of employees will be improved through enhanced training in cooperation with industries and exchanges the staff with MHLW, universities, and research institutes in Japan and overseas.

(2) Streamlining the review process (de facto review before application), and improving the necessary system (use of pre-application consultation)

- Regarding the pre-application consultation allowing for rolling assessment based on data that can be submitted from the development stage, which is de facto review before application, appropriate structure will be systematically strengthened, and all the requested consultations for excellent drugs with high medical needs will be accepted by 2018, taking into account the introduction of the SAKIGAKE Designation System.
- The acceptance range for the application dossier in English will be considered toward extension. Moreover, to foster skilled human resource with international business sense, training programs or opportunities will be created; for example, to involve the staff in international meetings or conferences for guideline development at the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) or the International Medical Device Regulators Forum (IMDRF), or to work for research at overseas organizations and graduate schools.

(3) Supporting the early practical application for innovative medical products through the introduction of the SAKIGAKE Designation System

- Among the pharmaceutical products, devices, and regenerative medicines targeting for the diseases that deem necessary to apply for the innovative treatments at the earliest possible time, when it demonstrates substantial improvement over conventional therapies in early clinical trials, for example, the phase 1 or 2a trials, it will be prioritized for consultation and reviews (e.g. prioritized consultation for clinical trials, pre-application consultation, and prioritized review) to accelerate the prompt practical application.

(4) Substantial post-marketing safety measures

- The medical information database is to be set up to expand the quality and quantity of data.

Also the environment for its use for risk-benefit evaluation of drugs using the accumulated data and for safety measures and related area will be developed. This may enable the analysis of information that are currently hard to estimate, for example, adverse effects with low incidence rate or analysis for each adverse effects to use as a reference for safety measures of future drugs. (shown again)

- Regarding the Risk Management Plan (RMP) that was implemented in April 2013 and is scheduled to be enacted in the GVP in October 2014, its preparation particularly for the innovative pharmaceutical products should be advised and supported. Further, information provision through the RMP will be encouraged. In addition, the use of pharmacoepidemiologic methods using the medical information database will be implemented as one of the safety monitoring activity methods in the RMP.
- The research of genetic markers and biomarkers related to the onset of serious adverse effects such as severe drug eruption will be promoted. Also, the evaluation of ethnic and regional differences in these markers will be conducted to utilize in post-marketing safety measures, based on the rate.
- Efforts to assure post-marketing efficacy and safety, such as streamlining post-marketing information collection and reducing its workload, will be made by building up a system of patient registry for the regenerative medicines and implantable medical devices and by collecting post-marketing safety information in cooperation with the pharmaceutical companies and related scientific societies.

3. Drug Pricing System

(1) Improving the predictability of the drug pricing system

- The Japanese drug pricing system has been highly rated because of its great significance in international settings in improving the predictability of market expansion after the development of new drugs. The development of new drugs targeted for unmet medical needs has increased and reviews for drug approval are performed in response to this trend. In these circumstances, it is important to improve the pre-approval predictability of the evaluation under the drug pricing system to encourage the early development of innovative medical products in Japan. Many initiatives have been introduced in the drug pricing criteria to date, such as the clarification of premium requirements or a rise in premium rates in the similar-efficacy comparison method, the introduction of adjustment rules for average operating margin used in the cost calculation method, and the trial introduction of a premium pricing scheme for the

promotion of new drug creation and resolution of unapproved drugs/off-label use.

- The introduction of the ‘SAKIGAKE introduction premium’ for drugs approved in Japan ahead of other countries and the increased rise in average operating margins used in the cost calculation method has been implemented in the reform of drug pricing system in 2014. Continuously the drug pricing system will be reviewed, taking into consideration the implementation of the early practical application for innovative pharmaceutical products, in view of the introduction of the SAKIGAKE Designation System.
- The research and development in Japan and the financial impact of the drugs that can contribute to a true improvement in the quality of medical treatment will be examined and confirmed, based on opinions of interested parties, for the ongoing provisional premium pricing scheme to promote new drug creation and resolution of unapproved drugs/off-label use. In addition, revision in the current pricing system, including appropriate items for the premium will be considered at the Central Social Insurance Medical Council.
- The predictability of premium rates in the drug pricing criteria will be improved by considering quantification methods for premiums in the similar-efficacy comparison method. Also, the quantification of correction factors for average operating margins in the cost calculation method will be considered.
- Currently, the PMDA has been providing Pharmaceutical Affairs Consultation on Research and Development Strategies as consultation for drug approval. In addition to this, consultations for drug pricing are also requested from some industries such as venture enterprises. Improvement in the predictability of drug pricing is important to let pharmaceutical companies develop drugs strategically. Therefore, a system in which a company can consult with the MHLW at any time will be examined on the details of existing price calculation rules, points to note, the prospects of prices according to stages such as before clinical trial, before regulatory review, and before inclusion on the drug price list to improve its predictability.

4. Improvements in the Infrastructure and Environment for Corporate Activities

(1) Strengthening industry competitiveness

- In order to strengthen the competitiveness of the Japanese pharmaceutical and device industries, it is important for both Japanese and foreign companies to perform active research and development thus providing attractive environment for drug discovery and medical device development in Japan. Although the industries have been supported by various policies

including tax incentives for research and development, investment in research and development by private enterprises should steadily be enhanced, facilitating the use of this support and continuously verifying its effectiveness. In addition, policies promoting the creation of intellectual property in Japan will be examined, verified, and analyzed referring to overseas policies.

- While the proportion of biopharmaceuticals such as antibody drugs in the pharmaceutical market has increased, delays in improving the infrastructure, e.g., small numbers of manufacturing bases for biopharmaceuticals in Japan, have been pointed out. Support for improving the infrastructure and environment, including the development of human resources for the discovery of innovative biopharmaceuticals from Japan will be considered.
- To develop medical devices with international competitiveness, it is necessary to undertake designing, trial manufacturing, and performance testing based on appropriate understanding of medical needs in Japan and overseas, and it is inevitable for the industry and the healthcare community to work cooperatively and share the cost, human resources, and technologies. To this end, training centers for human resources capable of developing medical devices through cooperation between industry and the medical community is established, to help them to discover and create marketable medical needs. Moreover, a support system (network) for the development of medical devices will be constructed along with the foundation of the Japan Agency for Medical Research and Development.

(2) Supporting small and medium enterprises (SME) and venture enterprises

- PMDA's Pharmaceutical Affairs Consultation on Research and Development Strategy (including onsite consultation) will be expanded to provide a clear guidance for innovative pharmaceuticals created by venture enterprises so as to accelerate practical application. Also, financial aid for examination fees will be considered. In addition, to support the medical device companies, many of which are SMEs, necessary measures will be taken with possible support measures, for instance, creation of new type of loan to micro businesses and individuals in the Japan Finance Corporation.
- Time to regulatory approval will be shortened by providing educational training regarding application for approval, clinical trial planning, and reliability standards such as GCP, for regulatory affairs staff in SMEs including new market entrants that develop software for medical devices or regenerative medicines, in order to accelerate documentation and improve the quality of application dossiers.

(3) Improving the environment for simultaneous international development

- The structure for Japan-led global clinical researches, such as international networks and support system under which Japanese clinical research institutions can participate in global clinical research, will be constructed so that Japan can demonstrate leadership in multi-regional clinical research to create innovative medical products originated from Japan and provide high-quality clinical evidence.

5. International Deployment

(1) Expanding in medical fields according to needs in export markets

- According to needs in emerging countries, corporate or medical professionals (e.g. MEJ (Medical Excellence JAPAN), JICA (Japan International Cooperation Agency), JETRO (Japan External Trade Organization)) and the relevant Ministries and Agencies should work together for global expansion. When Cabinet Ministers travel overseas, such opportunities will be leveraged for top-down sales. Moreover, from the viewpoint of disseminating high-quality Japanese healthcare services, policies promoting the export of pharmaceuticals, medical devices, and infrastructure will be steadily considered in light of the export markets.
- For developing countries where support to construct a healthcare system is needed, a system under which people in export countries can access broadly and appropriately to healthcare and afford those medical expenses (universal health coverage) will be introduced by transferring the experience and knowledge about Japan universal health insurance coverage. Also, the development and dissemination of pharmaceuticals and medical devices will be supported by Japanese companies, taking into consideration the levels of income and healthcare professionals in export countries.
- The pharmaceuticals and medical devices approved in Japan will be introduced in the targeted countries through interactions with local regulatory agencies in the countries or regions, particularly in emerging and developing countries, with cooperation between Japanese companies and relevant organizations (e.g. JETRO) that have overseas offices. Through these activities, mutual understanding of the process from development to approval will be promoted, and exports of pharmaceuticals and medical devices will be expanded through joint efforts by the Government and private enterprise. In particular, the research and development of pharmaceuticals products will be enhanced in cooperation with Asian countries, where there are relatively few ethnic differences, and the active expansion of the pharmaceutical product market will be sought.

(2) Improving the environment for international deployment

- Japanese company-led global expansion through promotion of international standardization for standards used in the regulatory system of each country will be supported, for instance by enhancing research into guidelines for evaluation of the efficacy and safety of drugs using the latest technologies or by proposing the international standards for the latest diagnostic and therapeutic techniques ahead of other countries.

- Activities related to regulatory harmonization for pharmaceuticals and medical devices will be promoted, and the environment for global business to the industries will be improved. For instance, the development of new guidelines is underway in regard to pharmaceuticals under the ICH, and the MHLW shall chair the IMDRF meeting in 2015 in regard to medical devices. For industry, the Japan Medical Imaging and Radiological Systems Industries Association (JIRA) shall chair the Global Diagnostic Imaging, Healthcare IT, and Radiation Therapy Trade Association (DITTA) meeting and Japan is the champion economy in multi-regional clinical trials under the APEC. Using these opportunities, Japanese government and companies shall work together to play a leading role in the international harmonization of regulations and standards.

- High-quality information about reviews and the post-marketing safety of drugs approved in Japan will be presented. For instance, company supporting activities such as releasing the English version of review reports and publishing the English version of package inserts (instructions and directions for use) and RMP prepared by pharmaceutical companies will be posted on the PMDA website. In addition, English materials for important information such as emergency safety information (yellow letter) and rapid safety communications (blue letter) distributed by the PMDA, as well as safety information such as the revision of precautions in package inserts will be released.

- With respect to the procedures for import and export of medical products, globalization of drugs originated from Japan will be supported through the streamlined digitization using the Nippon Automated Cargo Clearance System (NACCS).

(3) Promoting global expansion using the global collaboration framework

- Joint government-private support for the research, development, and supply of pharmaceuticals for developing countries, such as those for treatment of neglected tropical diseases, will be enhanced, using the excellent research and development capability of the Japanese

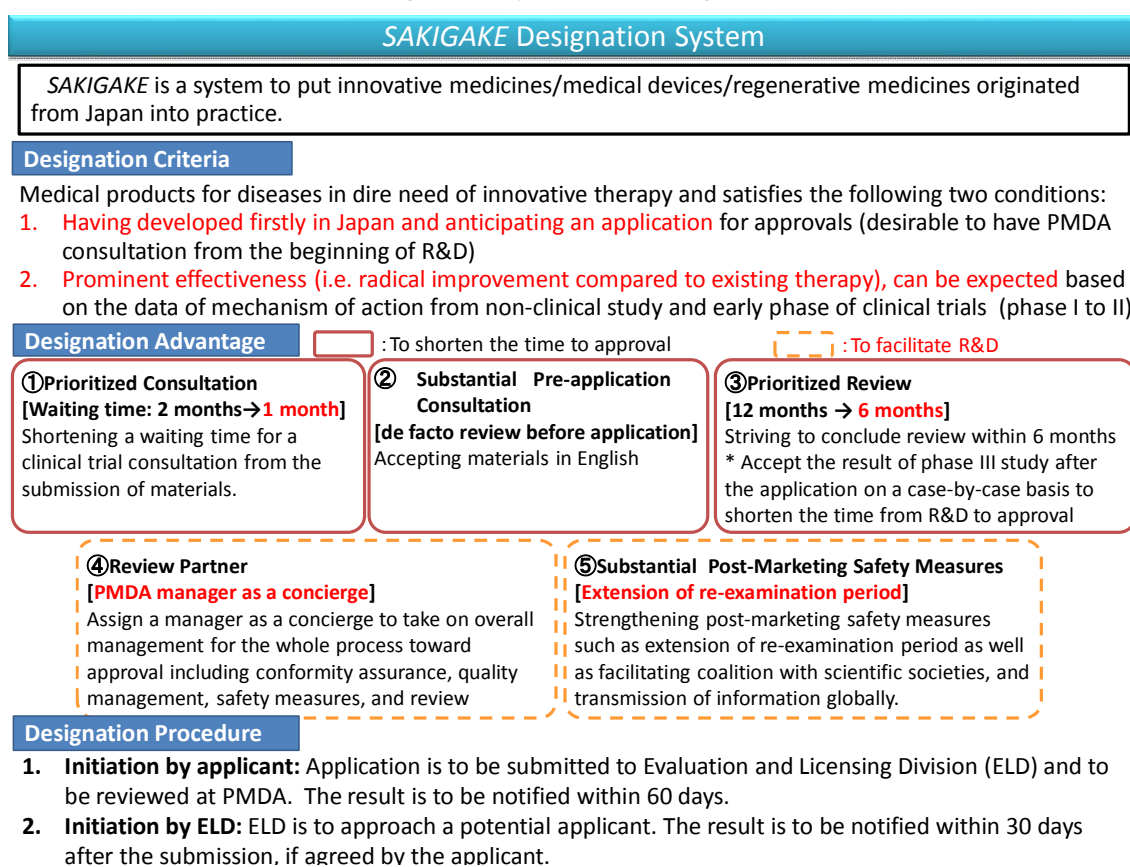
pharmaceutical industry, so as to contribute to international public health and the reliability and popularity of Japanese pharmaceutical companies and underpin global expansion.

- Expansion of exports after familiarization with prescription and procedures in regard to good Japanese pharmaceuticals and medical devices during the personnel collaboration, such as sending experts and accepting trainees, using public funds such as ODA (Official Development Assistance) for developing countries. Moreover, the stabilization of societies, particularly in the Western Pacific regions, should be achieved through improvements in public health standards through WHO supporting projects. With these efforts, the environment for Japanese pharmaceutical companies will be improved, so as to expand their operation into those regions.

III. Specific Cases of Creating Innovative Medical Products

SAKIGAKE Designation System and the scheme for rapid authorization of unapproved drugs, which are the core of the strategy of SAKIGAKE as a package, are described below. Promotion of practical application for innovative medical products is expected, using these plans.

(1) Supporting the early practical application for innovative medical products through introduction of SAKIGAKE Designation System (shown again)

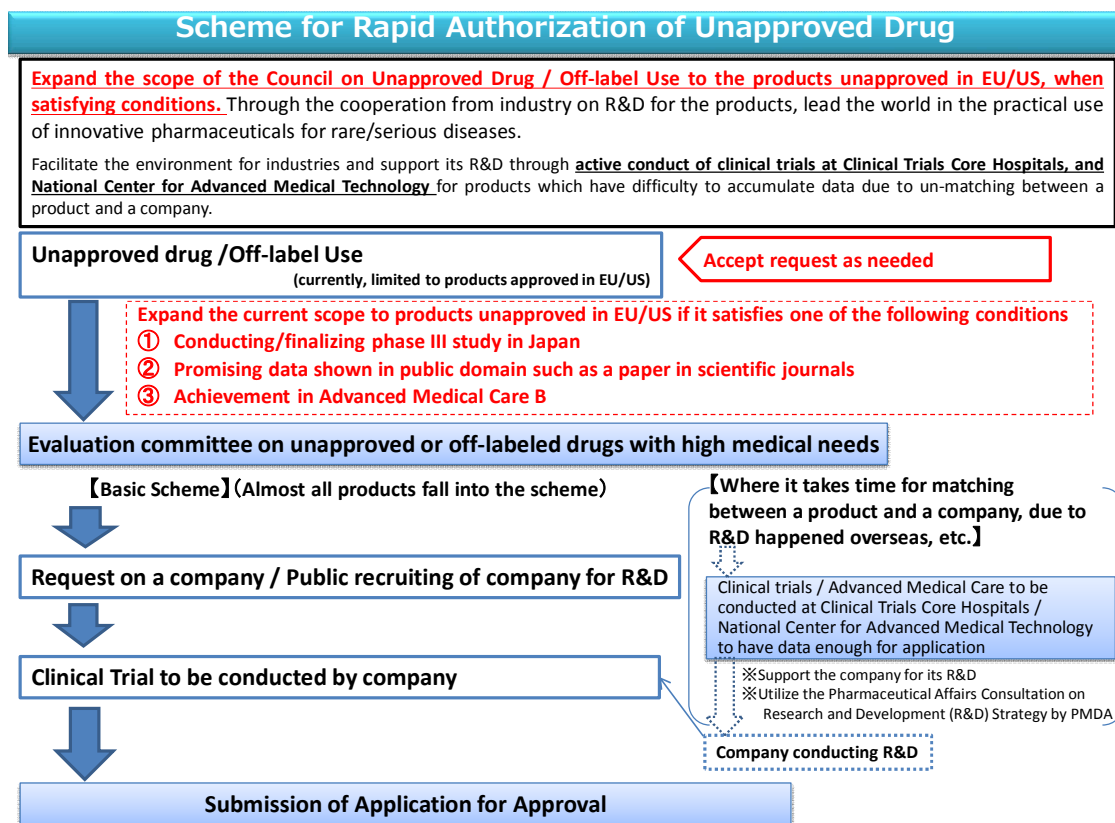


- Taking into account the fact that the early introduction of innovative pharmaceuticals, medical devices, and regenerative medicines is desired for diseases that deem necessary to apply for the innovative treatments at the earliest possible time, development in Japan should be enhanced by implementing all relevant policies, so as to achieve the early practical application originated from Japan ahead of other countries. Specifically, a compound which showed marked efficacy for targeted diseases based on early clinical trial data in phase 1 or 2a trials and to be developed and applied in Japan ahead of other countries (desirable if these have consulted with the PMDA) should be designated as the target drug for the SAKIGAKE Designation System and subject to consistent full support from development to launch so as to achieve faster practical

application.

- Producing innovative pharmaceutical products ahead of other countries with the shortest possible development and review process should be aimed through the designation system in which the following measures shall be used: 1) consistent prioritized consultation by the PMDA, 2) pre-application consultation in which de facto review is started with data that can be submitted before the application for approval, 3) prioritized review aiming for a further reduction in the total review period, 4) Assigning a manager as a concierge to take on overall management for the whole process toward approval including conformity assurance, quality management, safety measures, and review, 5) strengthening post-marketing safety measures including the extension of the reexamination period.

(2) Scheme for rapid authorization of unapproved drugs (shown again)



- The scope of the Council on Unapproved Drugs/Off-label use will be extended to include the drugs unapproved in Western countries that meet certain conditions, and request to develop such drugs will be made, in order to accelerate the practical application for drugs for the treatment of serious and life-threatening diseases ahead of other countries.

- To be specific, the scope of the Council on Unapproved Drugs/Off-Label use will be expanded to include drugs for the treatment of serious or life-threatening diseases even though they are unapproved in Western countries provided the following conditions are met: 1) a phase 3 trial in Japan is ongoing or has completed, 2) promising data shown in public domain such as a paper in scientific journals, and 3) sufficient records of use in the Advanced Medical Care B program. If there is a Japanese company developed these drugs, they will be requested to develop these indications and conduct company-sponsored clinical trials. If the drugs were developed by overseas venture enterprises and it will take time to accumulate data due to un-matching between a product and a company in Japan, research and development will be supported and the development environment should be facilitated by the active collection of data from investigator-initiated clinical trials or advanced medical care conducted at Clinical Trial Core Hospitals and the National Center for Advanced Medical Technology, and those data can be used for application for regulatory approval.