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Abstract

Japan's cabinet has been pushing forward with economic policy known as Abenomics since December 26 in 2012. Abenomics also includes the promotion of R&D in the medical field and related legislative reforms. The Headquarters for Healthcare and Medical Strategy Promotion was established in the cabinet in 2013. In 2014, "Act to Promote Healthcare and Medical Strategy" was promulgated and included for the formulation of the Health and Medical Strategy, the creation of the Plan for Promotion of medical R&D by the Headquarters, and the newly establishment for Japan Agency for Medical Research and Development. In 2014 the Pharmaceutical Affairs Law was revised and it newly contains the strengthening of safety measures for pharmaceuticals and medical devices, the construction of regulations taking into account the characteristics of medical devices, and a new definition for regenerative medicine along with approvals for manufacturing and sales in light of its special characteristics. Further, "Sakigake Package Strategy" formulated in 2014, which included an "advanced review designation system" as a fast-track- applications. With only three years having passed since the implementation of the policies related to Abenomics in 2013, it may be premature to judge their outcome, but several positive signs are appearing.

Key words: Abenomics, policy reform, health policy, medical R&D, innovation

1. Introduction

Japan's cabinet, led by Prime Minister Shinzo Abe, who took office on December 26, 2012, has been pushing forward with the policies known as Abenomics, with the goal of overcoming deflation and creating sustained economic growth. Abenomics is composed of the three "arrows" of a bold monetary policy, a flexible fiscal policy, and growth strategies to spur private investment, with somewhat of an emphasis on economic policies.

Abenomics also includes the promotion of R&D in the medical field and related legislative reforms [1]. The "Japan Revitalization Strategy" (adopted by the cabinet on June 14, 2013), states the following: "aims to simultaneously implement the securement of social security sustainability, the provision of high-quality healthcare services and the vitalization of the health industry [2]."

It also lays out major policies for the first stage, including "establishing control tower functions in medical R&D to accelerate practical application of innovative medical technologies," "significantly broadening the scope of advanced healthcare services," and "regulatory and institutional reform to accelerate the development of

pharmaceuticals and medical devices and regenerative medicine research.” Work had already started on policies related to these in 2013-2014.

This paper shows what policies have been implemented, and makes conjectures about the effects of the promotion of medical R&D and regulatory reform under Abenomics.

2. Establishment of the Control Tower Function for medical R&D

In August 2013, the Headquarters for Healthcare and Medical Strategy Promotion was established in the cabinet, with Prime Minister Shinzo Abe as Director, to serve as a control tower for the promotion of growth strategies for health, medicine and medical R&D. The Headquarters for Healthcare and Medical Strategy Promotion held discussions through the Expert Panel on the Promotion of Health and Medical Strategies, and in January 2014 compiled and published a report entitled “The Plan for Promotion of Medical Research and Development [3].” The report was positioned in order to contribute to the creation of new R&D institutions for promoting medical research fields to be prioritized under the Japan Revitalization Strategy.

In addition, the “Act to Promote Healthcare and Medical Strategy,” promulgated in May, 2014, provided the legal basis for the establishment of the Headquarters for Healthcare and Medical Strategy Promotion [4]. This law provided for the formulation of the Health and Medical Strategy, the creation of the Plan for Promotion of medical R&D by the Headquarters for Healthcare and Medical Strategy Promotion, and laid down the role of the newly established Japan Agency for Medical Research and Development (AMED).

AMED was launched on April 1, 2015, as an organ to carry out core roles in R&D support and environmental improvements in the medical field, based on the Plan for Promotion of medical R&D created by the Headquarters for Healthcare and Medical Strategy Promotion. The primary role of AMED is to carry out seamless, integrated research management from basic research to the point of deployment in society, transcending the boundaries of the major three ministries (MEXT: Ministry of Education, Culture, Sports, Science and Technology; MHLW: Ministry of Health, Labour and Welfare; and METI: Ministry of Economy, Trade and Industry) which encompass diverse fields from research in the health and medical field to practical application in society. Since in the past the promotion of R&D in the health and medical field was carried out by three ministries separately, this should be a great challenge for Japan.

3. Regulatory Reform to Reflect Patient Needs in Medical R&D

The “Implementation Plan for Regulatory Reform,” adopted by the cabinet on June 24, 2014, lays out priorities for regulatory reform in the health and medical field [5]. It includes “creating a new mechanism for incorporating treatments not covered by medical insurance” as a topic related to clinical research in cutting-edge science and technology.

This refers to creating “patient-requested therapies” as a new mechanism within medical treatment combining non-covered treatments (taking effect in April, 2016). Originating from a request by a patient with cancer or similar intractable disease, this mechanism allows the rapid implementation of combined therapies

including non-covered treatments such as domestic non-approved pharmaceuticals not currently covered by insurance, and off-indication use (use of pharmaceuticals for a purpose other than the indications for which its manufacture and sale were approved) of pharmaceuticals approved domestically. This is also a big change, because treatments subject to public insurance and mixed treatments using free combinations of treatments which were not-eligible for insurance had not been allowed, excluding certain exceptional cases (advanced medical care services etc.).

In this way, regulatory reform was implemented to allow the undertaking of advanced healthcare services depending on patient needs.

4. Regulatory and Institutional Reforms to Accelerate Innovative Medical R&D

Reforms to laws and regulations concerning the safety of pharmaceuticals and manufacturing and sales approvals are essential to realize the “Japan Revitalization Strategy” for accelerating the development of innovative pharmaceuticals, medical devices, and research in regenerative medicine.

The Pharmaceutical Affairs Law was revised in 2014 and renamed to “The Law on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices.” It newly contains the strengthening of safety measures for pharmaceuticals and medical devices, the construction of regulations taking into account the characteristics of medical devices, and a new definition for regenerative medicine along with approvals for manufacturing and sales in light of its special characteristics.

In the revised Pharmaceutical Affairs Law, regenerative medical products are defined as “processed (e.g. cultured) human cells which are used for the purpose of rebuilding structures and functions of the human body and treating and preventing disease, and/or products introduced into human cells for the purpose of gene therapy.” It also states that both of these “possess special characteristics of non-uniform quality making it difficult to predict their effectiveness, because of the use of human cells.” Because of these characteristics, if their effectiveness can be inferred and their safety ensured, they may be approved for conditional and time-limited manufacture and sale.

Since in the past there was no law providing for the safety of regenerative medical products, the “Act on the Safety of Regenerative Medicine” was newly established (taking effect on November 25, 2014). This law provides standards for institutions providing regenerative medicine and cell culture facilities, in order to ensure safety when carrying out clinical research on regenerative medicine and implementing advanced healthcare services [6].

In addition, based on the Japan Revitalization Strategy and the Health and Medicine strategy, the MHLW launched a project team within the ministry to lead the world in the practical application of innovative pharmaceuticals, formulating its “Sakigake Package Strategy [7]” (June 17, 2014), a strategy packaging basic research to clinical research and trials, approval reviews and safety countermeasures, insurance eligibility, basis for corporate activities and setting up of environments, and international expansion. Also included was an “advanced review designation system.”

This designates those pharmaceuticals, medical devices, and regenerative medical products targeting patients who want these revolutionary therapeutic methods to be available for use as soon as possible, and which promises large improvements over existing therapies based on initial clinical trial data (phase I or early phase II trials),

giving them priority for clinical trial consultations and review, with the aim of bringing them into actual use as promptly as possible. This was implemented on a trial basis on July 1, 2015.

5. Revision of Ethical Guidelines on Clinical Research

In the EU, the EU Clinical Trials Regulation EU No 536/2014, which is expected to come into effect by October, 2018 [8], was created in 2014. The existing EU Clinical Trial Directive covers all clinical trials using pharmaceuticals, not only clinical trials for the purpose of regulatory approval, but includes clinical research carried out by university researchers. As a Regulation unlike a Directive cannot be replaced by a domestic law in each EU country, the change from the Directive to the Regulation was to raise the level of regulation. However, while the Directive covered pharmaceuticals whose safety had already been confirmed, the new Regulation will relax the process for low-risk clinical trials [9].

In Japan, by contrast, a clinical trial carried out by a university researcher not for the purpose of regulatory approval, even if using pharmaceuticals, is not regulated by law. Instead, ethical guidelines have been established which are to be observed by those carrying out the clinical research.

The MEXT and the MHLW, noting the commonalities in their ethical guidelines as research grew more diverse, combined the “Ethical Guidelines for Epidemiologic Research (MEXT and MHLW), defined in 2002 and revised in 2007, and the “Ethical Guidelines for Clinical Research” (MHLW), defined in 2003 and revised in 2008, to create a new ethical guideline which was promulgated in 2014.

It was the “Ethical Guidelines for Medical Research on Human Subjects [10]”, which took effect on April 1, 2014, which included new provisions clarifying the responsibility of the heads or chief researchers at research institutions, strengthening the functions of ethical review committees and ensuring the transparency of reviews, provisions relating to informed consent and personal privacy, provisions related to the management of conflicts of interest, provisions related to the archival of research-related information and materials, and provisions for the monitoring and oversight of those responsible for research.

In addition, the MHLW abolished the “Guidelines for Gene Therapy Clinical Research” set forth in 2002 by the MEXT and the MHLW and revised in the new “Guidelines for Gene Therapy Clinical Research” (announced on August 12, 2015). These guidelines modified the definition of “gene therapy” to “injection of genes or cells into which genes have been introduced for the purpose of treating and preventing disease,” including prevention as a new purpose. Furthermore, whereas the old guidelines had defined the targets of clinical research as “severe hereditary diseases, life-threatening diseases, and diseases which significantly impair bodily function,” this phraseology was removed, greatly broadening the diseases subject to research.

The revision of ethical guidelines, which may have been influenced by Abenomics but is not part of it, was implemented at the same time, and appears to have served to steadily advance cutting-edge medical R&D.

6. Conclusion

With only three years having passed since the implementation of the policies related to Abenomics in 2013, it

may be premature to judge their outcome, but several positive signs are appearing.

On September 18, 2015, under the revised Pharmaceutical Affairs Law, two human somatic stem cell processed products were approved as a regenerative therapy product. One is human bone marrow-derived mesenchymal stem cells for treating acute graft-versus-host disease after hematopoietic stem cell transplantation (rapid onset GVHD); the other is skeletal muscle-derived cell sheets for treating severe heart failure due to ischemic heart disease [6, 11]. The latter is a conditional and time-limited approval. Previous to the revision of the Pharmaceutical Affairs Law there had been only two regenerative medical products approved for manufacture and sale, the autologous cultured epidermis in 2007 and the autologous cultured tendon in 2012. Based on this, we can infer that the speed of moving from research to use in the real world has become faster.

In addition, until March in 2016, total 11 products [12], of which six are pharmaceuticals, two medical devices, and three regenerative medical products, subject to the “Advance Review Designation System.” Five of them were developed by industry-university joint research or originally university research. Since the number of investigator-initiated clinical trials in Japan was relatively low compared with other countries [13], the system might lead to improve the number by incentive for shortening examination time.

Furthermore, on May 13, 2016, Clinical Trial Law was submitted to the Diet. Although the bill is under deliberation, sooner or later “Ethical Guidelines for Medical Research on Human Subjects” will be replaced by the new law.

We might keep a careful eye on not only the policy trend of the promotion of medical R&D and institutional reforms under Abenomics, but also on its social outcome.

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