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STATEMENT / OPINION

Finding the Optimal Regulatory Systems to Facilitate the Development of Novel and Advanced Therapeutics

Shoji Sanada, MD, PhD

Recent accelerated progress in the development of a dramatically increasing number of therapeutic medicines, devices and techniques is strongly leading to advanced medical markets, which in turn give physicians a wide variety of effective therapeutic options in daily medical practice.[1] It is also leading, however, towards more cross-sectional techniques, as well as to comprehensive or integrative medicines and devices, which are often beyond the existing regulatory systems.

To deal with this overwhelming and inevitable global trend, prompt, effective and generally accepted regulations are continuously needed to not only make all such developments effective and safe in every instance, but also to ensure rapid access for each patient eagerly awaiting more effective and personalized therapies.

A promising movement to expedite the marketing process is inter-regional harmonization of the process for pharmaceutical approval, that is, the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use, known as ICH, which aims to create globally standardized uniform regulations to facilitate rapid and simultaneous global access to novel qualified therapeutic technologies.

Meanwhile, the Japanese government has established a variety of unique and specific medical policies and regulations to facilitate innovation of therapeutic technologies.

As standard, all citizens in Japan are primarily covered by official health insurance for pharmaceutically approved treatments carried out and prescribed by officially registered health insurance doctors, a system that is known as universal health insurance coverage. Countries other than Japan that use this system are still rare, and even fewer also assure free access to any hospital. In contrast, to be reimbursed from the official health insurance, health insurance doctors are required to comply with the Rules for Therapeutic Operation and Insurance Coverage attached to the Health Insurance Law, which prohibits the performing of special or novel therapies, prescribing or dosing of agents

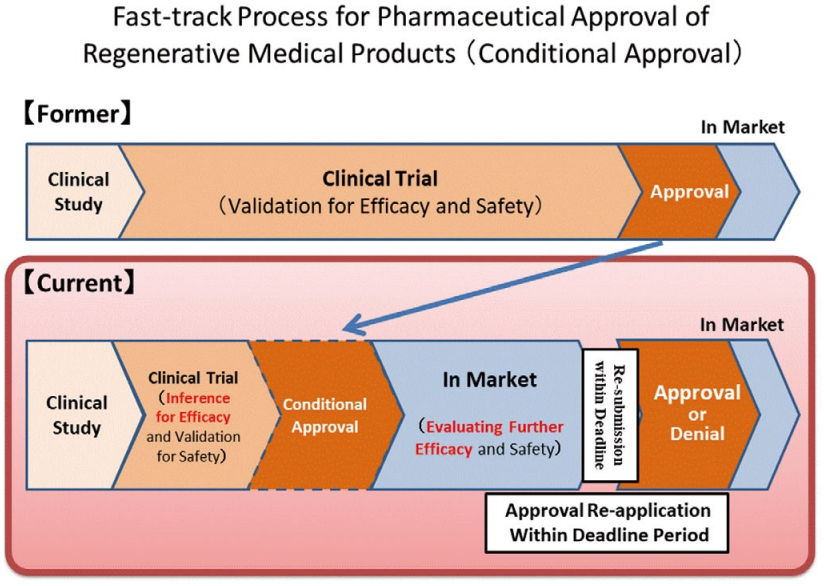

Figure 1. Introduction of "Conditional Approval with Post-commercialization Evaluation" in regenerative medicine. (Reproduced from public open data issued by the Ministry of Health, Labour and Welfare, Japan.)

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Academic Clinical Research Center, Department of Medical Innovation, Osaka University Hospital, Suita; Department of Cardiovascular Medicine, Osaka University Graduate School of Medicine, Suita, Japan
Mailing address: Shoji Sanada, MD, PhD, Academic Clinical Research Center, Department of Medical Innovation, Osaka University Hospital, 2-2 Yamada-oka, Suita 565-0871, Japan. E-mail: s-sanada@cardiology.med.osaka-u.ac.jp
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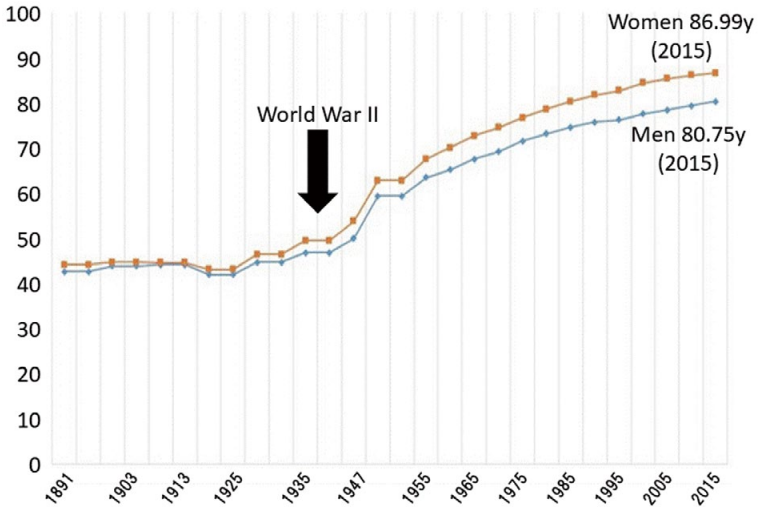

Figure 2. Change in the mean lifespan of Japanese men and women. (Reproduced from The Lifespan Chart, public open data issued by the Ministry of Health, Labour and Welfare, Japan.)

other than those officially assigned, or performing any clinical tests for research purposes. Hence, given that primary health insurance applies only to treatment that involves products with official approval of efficacy and safety, and because it generally does not allow mixed billing for combined treatments composed of therapies with and without pharmaceutical approval, the end result would be total disqualification from health insurance coverage.

There are some exceptions, however, to mixed billing claims: that is, partial overage by health insurance of the treatment with pharmaceutical approval, combined with total billing of the patient for the treatment without pharmaceutical approval. The Healthcare Services for Assessment is one such program, defined in the Health Insurance Law as applying to advanced or novel therapies that need assessment for efficacy, safety and prevalence to claim coverage by official health insurance. Healthcare Services for Assessment consists of clinical trials, the Advanced Medical Care Program, and health-care services based on patient application. Clinical trials are studies complying with the Pharmaceutical Law and progressing towards pharmaceutical approval in the conventional fashion, whereas the Advanced Medical Care Program might be defined as clinical studies that comply with the Official Ethical Guidelines for Medical Studies in Humans, or the new Clinical Research Law. In addition to having a mixed billing system, the Advanced Medical Care Program has another advantage in that once a treatment in the program is completed and its efficacy has been successfully appealed, it becomes eligible for the Governmental Review Conference for Fast-track Approval. When products are certified as valuable and sufficiently accountable to be approved without clinical trials, they are directly approved. Also, when the benefit of a therapy is not considered as evident but is considered valuable enough to warrant clinical trials, the government urges the companies to develop such therapies for Pharmaceutical Approval.

Another notable unique regulation to accelerate clinical development is the so-called "Conditional Approval with Post-commercialization Evaluation". This was first launched in 2013 when the Pharmaceutical Law was revised to facilitate pharmaceutical development of regenerative products. Briefly, although conventional pharmaceutical approval needs proof of concept for efficacy and safety, the current law allows for conditional approval of regenerative medical products when the inference for efficacy as well as validation of safety have been achieved. Then, the authority sets a period that allows a product to be released onto the market with further full approval, conditional on efficacy and safety studies while commercially available (**Figure 1**). This idea has been tested in advance in some fields,[2] but appears to be so groundbreaking that some researchers have voiced serious concerns about it,[3] partly because regenerative medicine is a new area and the schemes for evaluating safety and efficacy, as well as consistent quality of the products (mostly from bioengineering processes), have not been established as yet, and it might also be difficult to plan double-blind randomized trials in this field.

All these regulations and rules were primarily designed to disseminate good health care or to facilitate rapid access to novel advanced medical therapies all across the country. Indeed, we can say that some of them have brought us historical success: the mean lifespan of the Japanese nation has been extended (**Figure 2**), leaping to the top in the world, and most of us are provided equally with thoroughly well-standardized medication for almost all types of diseases under public insurance coverage. It is also true, however, that the regulatory environment has become so unique and diverse that it does not necessarily stand aligned with global trends, and people in other countries often say that they are not familiar with specific Japanese regulations. One reason for this diversity might be that our health-care and pharmaceutical approval systems are unique, and another reason might be that our regulations cannot keep up with the rapid progress in medical science and can only follow with patchy rules, such that they become rigid and inconsistent with each other.

In addition, there might be field-specific issues. We in the cardiovascular field are especially familiar with the difficult issue of needing huge clinical studies with longer terms and greater numbers of participants to get proof of concept, which makes clinical research and development in this field very challenging, stemming from issues of study design, surrogate markers, and research approaches to testing novel

therapeutic principles.[4] Moreover, we also have issues regarding how we develop and manage access to orphan drugs.[5]

Although there have been some advanced attempts, we obviously need more revolutionary ideas to deal with the many difficulties in regulations, rules and study designs. It is timely that we can now rigorously discuss such issues in this ground-breaking Journal, *Circulation Reports*.

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