Interaction Analysis between Innovation and Regulation: The Concept of Regulatory Science as a Process (RaaP) and Its Applications

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Abstract--**The jurisdiction against emerging technologies is a core process for designing "Technology Management for Social Innovation." The concept of "Regulatory Science" (RS) in technology jurisdiction has a diverse range of meanings among its users in the medical field. Thus, the analysis of interactions between innovation and regulation is not generalized and includes systematic approaches. RS is categorized as "a third-party science," differing from a basic science or an applied science, and is recognized as constituting "adaptive activities" against innovator's activities.**

This study proposes the concept of "Regulatory Science as a Process" (RaaP), to analyze interactions between innovators and regulators by identifying process–process interactions. RaaP is defined by the total process of regulator's policy value chains, which includes activities upstream of technology jurisdiction, technology forecasting to technology prioritization, research and development for rule making, rule making, international harmonization, optimizing organization, draft rule operation, monitoring, and revision. Based on an analytical framework for interaction between RaaP and the innovation process, two case studies in the medical field, namely the collaborations of the US National Institutes of Health–Food and Drug Administration (NIH–FDA) and the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) with innovators, were conducted to validate the process–process interaction analysis and RaaP concept.

I. INTRODUCTION

On November 20, 2013, the Japanese Diet passed the Act titled Ensuring of Safety of Regenerative Medicine (the Regenerative Medicine Law) and made amendments to the Pharmaceutical Affairs Law (the new PAL under the Pharmaceutical and Medical Device Act), as both regulations apply to drugs, medical devices, and regenerative medicine. Both laws came into effect in November 2014, providing broad possibilities to develop new medical products, especially with regard to regenerative medicine, and to permit their reviews by regulators and/or related scientists [1]. However, there were no efforts to analyze the reform from the social science perspective, including the analysis of policymaking processes and international comparison.

On the other hand, as an integrated funding agency in the health care field, the establishment of the Japan Agency for Medical Research and Development (AMED) would facilitate investments from basic research to translational research, and thus, the Japanese regulators should prepare themselves on how to treat upcoming emerging technologies and examine how they may be regulated [2].

Faulkner [3] proposed that ideally, a social scientist's contribution is to provide a new framework to change the situation from "innovation-first/regulation-after" to "co-development of the regulatory arena and novel technology." Indeed, the question of whether social science perspectives could contribute to minimize the time lag after the invention, keeping safety and efficacy in mind, remains to be answered. Notably, to realize "co-development," observations of phenomena on both the innovator's side and the regulator's side in the early phase of the emerging technology would be a key to understanding these interactions. To address this issue in this study, I propose a definition of the regulator's total process and provide a new framework to analyze interactions between innovators and regulators.

II. LITERATURE REVIEW

This study considers the following themes in the research literature: (1) definitions of regulatory science and (2) analysis of the regulatory process.

A. Definitions of Regulatory Science

The term "Regulatory Science" (RS) is a key word used to handle the regulatory process of technology and varies widely with persons, times, and regions. Uchiyama [4] first defined the term in Japan in a broad sense and noted that "regulatory science is the science of optimizing scientific and technological developments according to objectives geared toward human health." This definition was easily modified by various people in many senses.

The usage of the term RS in the US also varies. Jasanoff [5] defined it as adaptive activities against "research science" and linked the term to the policymaking process. Concepts resembling RS, such as trans-science [6], mandated science [7], post-academic science [8], and mode 2 science [9], have risen and invoked discussions on their dissimilarities. In 1998, the American Association of Pharmaceutical Sciences (AAPS) defined RS as "a complex integration of regulatory research and regulatory affairs."

All the concepts and definitions of RS and concepts akin to it in both Japan and the US were defined in the form of sentences and not as total regulatory processes that include upstream as well as downstream elements of regulatory activities. As the AAPS defined RS as "research" and "affairs," the problems associated with this term arise from the fact that RS itself is not only a pure science-related research activity but also includes process-related regulatory affairs. Thus, the solution to this issue is that a practical definition of RS should be a process-based definition including both research

activity for rule making and real regulatory activities within the processes.

B. Analysis of the regulatory process

Many researchers have tried to describe the regulatory process and regulatory space with specific conceptualizations. For the petrochemical field, Barry [10] proposed a "Technological Zone" composed of three parts, namely, the metrological zones, infrastructural zones, and zones of qualification. Faulker [3] applied the concept of "Technological Zone" to explain situations in regenerative medicine. Hogarth [11] introduced the concept of "Pre-regulatory Space" to explain the voluntary genomic data submission system in the US and discussed the interaction between non-validated data collection and regulatory activities before creating a guideline. Cambrosio et al. [12] regarded a total system in the medical field as a "Biomedical Platform," and Wilson-Kovacs et al. [13] proposed "ongoing, deliberative regulatory space between different stakeholders (including regulators and clinical teams)" based on case studies in cardiac stem cell research. The above-mentioned proposed concepts are rather static explanations, do not cover the total regulatory process, and sometimes lack dynamic perspectives.

On the other hand, Wild et al. [14] introduced the concept of "Horizon Scanning Systems" (HSS), which covers activities from upstream to mid-phase regulatory processes. HSS define five processes, as follows. (1) Identification (and filtering): identify new and emerging technologies, gather basic information on the technologies, and their applications; (2) Prioritization: select the most important technologies for assessment (priority setting) and filter out unimportant technologies as well as worthless information; (3) Early assessment: perform assessments of selected technologies; (4) Dissemination: disseminate information on important technologies to target audiences; and (5) Monitoring: monitor assessed technologies, and update reports if new information is available. They conducted a literature survey based on the HSS concept and identified 13 cases. HSS is a good sample to describe the regulatory process from its starting point and can help us consider how we could change from "innovation-first/regulation-after" to "co-development of a regulatory arena and novel technology," especially focusing on the early phase of an emerging technology. However, HSS does not cover the downstream activities of rule making itself, and processes after rulemaking such as monitoring the functions of the rules and interactions with sponsors (innovators). Another aspect that must be considered is how to describe the interaction between innovators' activities and regulators' activities. It is necessary to observe both activities simultaneously in the same framework for understanding these interactions. Thus, we need to set the innovator's process with the regulator's process in the same framework.

III. RESEARCH OBJECTIVE AND ANALYTICAL FRAMEWORK

A. Objectives

The objective of this study is to propose a novel framework for evaluating interactions between innovators and regulators by defining Regulatory Science as a Process (RaaP) and by co-setting both innovators' processes and regulators' processes in the same framework, to analyze process–process interactions and to apply the framework to cases.

B. Policy value Chain of the regulatory process

The total process (upstream to downstream activities) of the regulator's policy value chains should contain the following.

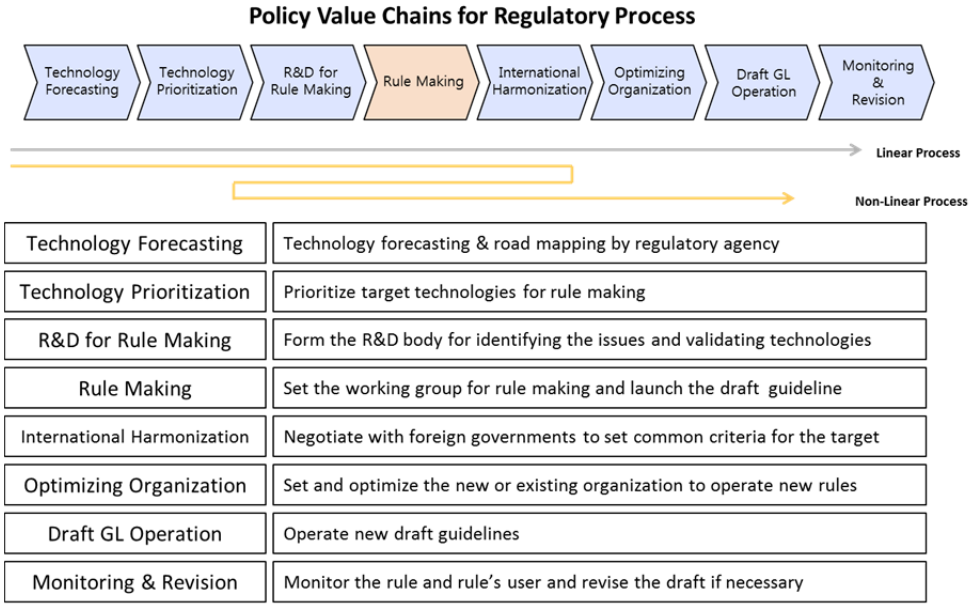
(1) Technology forecasting by the regulator, **(2) technology prioritization** for rule making, **(3) research and development for rule making,** which comprises deciding research project settings for data gathering to make a rule and validate the technologies, **(4) rule making,** which includes setting the working group for rule making and launching the draft guideline, **(5) international harmonization,** which constitutes negotiations with foreign governments to set common criteria for the target technology, product, or therapy, **(6) optimizing organization,** which includes setting and optimizing new or existing sections/organizations to operate the new rules, **(7) draft guideline operation,** which helps operate the new draft guidelines, and **(8) monitoring and revision,** wherein the rules' users are monitored, and the draft is revised as needed (Fig.1).

These total processes normally run in a linear, and sometimes non-linear, fashion depending on the situation. By defining the regulatory activities within a process, we can recognize the total functions of regulatory science, and therefore call this value chain RaaP. Although science obviously refers to scientific activities, RS includes not only science for rule making but also includes activities beyond "science." It covers broad activities, from finding target technologies to rule operation for new products.

C. Analytical framework for Interactions between the Innovator's process and the regulator's process

The second step in constructing a framework is to address how the innovator's processes in the medical field interact with the processes of the regulatory value chains seen in Fig.1.

Definitions pertaining to the innovator's processes: (1) New Principle: a starting point wherein a scientifically or technologically new theory and/or phenomena that is/are discovered or invented could potentially be utilized in the medical field, **(2) Discovery Research:** new principle is investigated further to propose a product concept, **(3) Animal Model/Proof of Concept (POC):** a product concept is evaluated using an animal model, and the POC is obtained, **(4) Selecting Regulatory Options:** innovators select a



Technology Forecasting	Technology forecasting & road mapping by regulatory agency
Technology Prioritization	Prioritize target technologies for rule making
R&D for Rule Making	Form the R&D body for identifying the issues and validating technologies
Rule Making	Set the working group for rule making and launch the draft guideline
International Harmonization	Negotiate with foreign governments to set common criteria for the target
Optimizing Organization	Set and optimize the new or existing organization to operate new rules
Draft GL Operation	Operate new draft guidelines
Monitoring & Revision	Monitor the rule and rule's user and revise the draft if necessary

Fig. 1 Total Policy Value Chains of Regulatory Science as a Process (RaaP)

regulatory path among the existing rules that control a product or service to be commercialized, **(5) Preclinical Study:** animal studies following Good Laboratory Practice (GLP) are conducted, **(6) Clinical Study:** human clinical trials based on the Guideline for Good Clinical Practice (GCP) are conducted, **(7) Filing and Approval:** the filing package is submitted to the regulator, and **(8) Marketing and Production:** this involves selling the product.

A framework to analyze interactions between the innovator's value chains and the regulator's value chains: The framework for interaction between the innovator's activities and the regulator's activities is proposed in Fig.2. An innovator's value chain and a regulator's process are arranged in parallel and linked to each other. For example, the processes of "New Principle" to "Animal Model POC" in the innovation process address the processes of "Technology Forecasting" to "Optimizing Organization" in the regulatory process (see the yellow arrows in Fig.2).

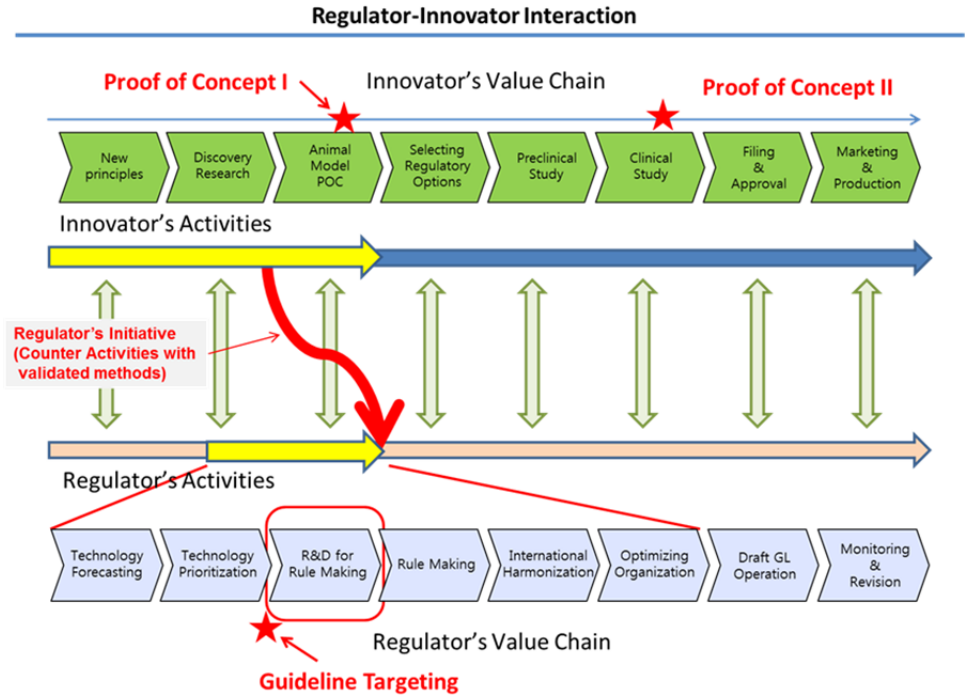


Fig.2 Framework for Regulator–Innovator Interaction Analysis

The process of "Selecting Regulatory Options" to "Marketing and Production" in the innovation process match the processes of "Draft Guideline Operation" to "Monitoring and Revision" in the regulatory process.

After "Discovery Research" is complete in the innovation process, regulators could recognize the possibility of developing products or services proposed by innovators and simultaneously set new targets for the guidelines (guideline targeting) if needed (see the red arrow in Fig.2) under the appropriate interactions. The regulator's initiative to start adaptive activities with validated evaluation methods against the innovator's outcome are necessary for detecting and prioritizing target technologies. Although many such activities have established regulatory initiatives, such as the Critical Path Initiative in the US [15] and the Innovative Medicine Initiative (IMI) in Europe [16], these activities have not been analyzed using the process-based approach. As shown by Wild et al. [14], who analyzed the technology selection process by breaking it down into its components, the regulator's activities could be recognized as comprising several processes. However, to observe the initial process concerning rule making within the regulator's process, we should also address the innovator's process. Notably, these early phase interactions between innovators and regulators are required for "co-development of a regulatory arena and novel technology," and the identification of emerging technologies by regulators is a trigger for generating new rules to regulate that technology. Thus, the analytical framework for these activities should include the definitions of both the regulatory process and the innovation process in a parallel and an interactive way. I name this action the "Regulator's Initiative." The regulator's initiative in the rule making process and the first POC in the "Animal Model POC" process target the new guideline, and thus, I call this phenomenon "Guideline Targeting." In addition, the framework for regulator–innovator interactions should also cover later processes such as rule making, and creating organizations to operate the newly formulated guidelines, and sometimes, an international harmonization process may be required to observe the total interaction process.

IV. CASE STUDIES

To analyze regulator–innovator interactions, this study focuses on the "Regulatory Initiative" and "Guideline Targeting" in early phase interactions (before rule making), and "Guideline Operation" in the later phase (after rule making). For this purpose, this study selects two cases from the US and Japan that have clear interactions between innovators and regulators, and applies the framework to these cases.

A. The NIH–FDA Joint Leadership Council in the early phase

1. Interaction Profile

The NIH–FDA Joint Leadership Council was established in 2010, and its purpose is as follows.

> "The National Institutes of Health (NIH) and the Food and Drug Administration (FDA) share a common goal of advancing public health by promoting the translation of basic and clinical research findings into medical products and therapies. The agencies are complementary in their roles and functions—NIH supports and conducts biomedical and behavioral research and FDA ensures the safety and effectiveness of medical and other products. The Joint Leadership Council will work together to help ensure that regulatory considerations form an integral component of biomedical research planning, and that the latest science is integrated into the regulatory review process. Such collaboration and integration will advance the development of new products for the treatment, diagnosis, and prevention of common and rare diseases and enhance the safety, quality, and efficiency of the clinical research and medical product approval enterprise. The formation of the Leadership Council represents a commitment on the part of both agencies to forge a new partnership and to leverage the strengths of each agency toward this common goal." [17]

The NIH and FDA set up four grant programs: 1) Accelerating Drug and Device Evaluation through Innovative Clinical Trial Design, 2) Replacement Ocular Battery (ROBatt), 3) Characterization/Bioinformatics-Modeling of Nanoparticle: Complement Interactions, and 4) Heart-Lung Micromachine for Safety and Efficacy Testing. With regard to the analytical framework, these four programs support both innovation and new regulations, and thus, the regulator–innovator interactions of the four programs refer to the interactions "before" the rule making processes (see the yellow arrows in Fig.2). This grant system is clearly in line with the "Research and Development for Rule Making" process within the regulatory process.

2. Case study: DARPA–FDA–NIH Microphysiological Systems Program for Safety and Efficacy Testing

The DARPA–FDA–NIH Microphysiological Systems Program includes the Heart-Lung Micromachine for Safety and Efficacy Testing project. It started in 2011 with the aim of supporting the development of human microsystems, or organ "chips," to screen swiftly and efficiently for safe and effective drugs (before human testing). This collaboration occurs through the coordination of three independent programs, The Engineering Platforms of the Defense Advanced Research Projects Agency (DARPA) and Biological POC at Harvard University (DARPA-BAA-11-73: Microphysiological Systems), NIH's Underlying Biology/pathology and Mechanistic Understanding (RFA-RM-12-001 and RFA RM-11-022), and FDA's Advice on Regulatory Requirements, Validation, and Qualification. The goal of the Integrated Microphysiological Systems for Drug Efficacy and Toxicity Testing is to develop in vitro microphysiological systems representative of major

organs/tissues in the human body, which will facilitate the assessment of biomarkers, bioavailability, efficacy, and toxicity of therapeutic agents prior to clinical trials. The goal of Stem/Progenitor Cell-Derived Human Micro-organs and -tissues is to develop stem- and progenitor-derived cell resources to seed circulatory, endocrine, gastrointestinal, immune, integumentary, musculoskeletal, nervous (including eye), reproductive, respiratory, and urinary microsystems.

On the other hand, the FDA and the Center for Drug Evaluation and Research (CDER) have launched a Draft Guidance on Qualification of Drug Development Tools [18]. The Drug Development Tool (DDT) Qualification programs provide a mechanism for formal review by the CDER to qualify new tools that would benefit drug development. Three projects have been implemented for biomarkers, clinical outcome assessments, and animal models, and the concept of the DDT should be applicable to any tool proposed for use in regulatory decision making. The Heart-Lung Micromachine for Safety and Efficacy Testing project is a potential candidate for the same. Once qualification is granted, a decision is publicly communicated in the form of guidance, and then any drug sponsor can submit data obtained with the qualified DDT without being asked for further evidence in support of its suitability [19]. Thus, Guidance on Qualification of Drug Development Tools is a sort of "guidance of guidance" for emerging technologies and is regarded "Guideline Targeting" in this study.

Fig.3 illustrates the framework analysis of the DARPA–FDA–NIH Microphysiological Systems Program for Safety and Efficacy Testing. Two projects, DARPA's engineering platforms and biological POC, and the NIH's underlying biology/pathology and mechanistic understanding, are regarded as activities corresponding to "New Principle" to "Animal Model POC," respectively, within the innovator's value chain. The FDA's advice on regulatory requirements, validation, and qualification is regarded as an activity to facilitate the qualification as "Regulator's Initiative." The DARPA–FDA–NIH collaboration aims to grant qualification for this technology, and the collaboration itself is regarded as an activity for "Guideline Targeting" to a specific goal, namely, to create a new guideline based on the "guidance of guidance," the Draft Guidance on Qualification of Drug Development Tools. Once qualification is granted by the FDA, the process proceeds to the next step: "Rule making."

B. PMDA's SAKIGAKE fast track designation in the later phase

1. Interaction Profile

On June 17, 2014, the Project Team at the Ministry of Health, Labour and Welfare (MHLW), Japan, formed the Strategy of SAKIGAKE with the objective of becoming a global leader in the practical application of innovative medical products [20]. This strategy was affected by the US FDA's fast track designation, namely the Breakthrough Therapy Designation and Priority Review Pathway [21, 22]. The SAKIGAKE Designation System is part of the Strategy of SAKIGAKE, and it accelerates the drug development and

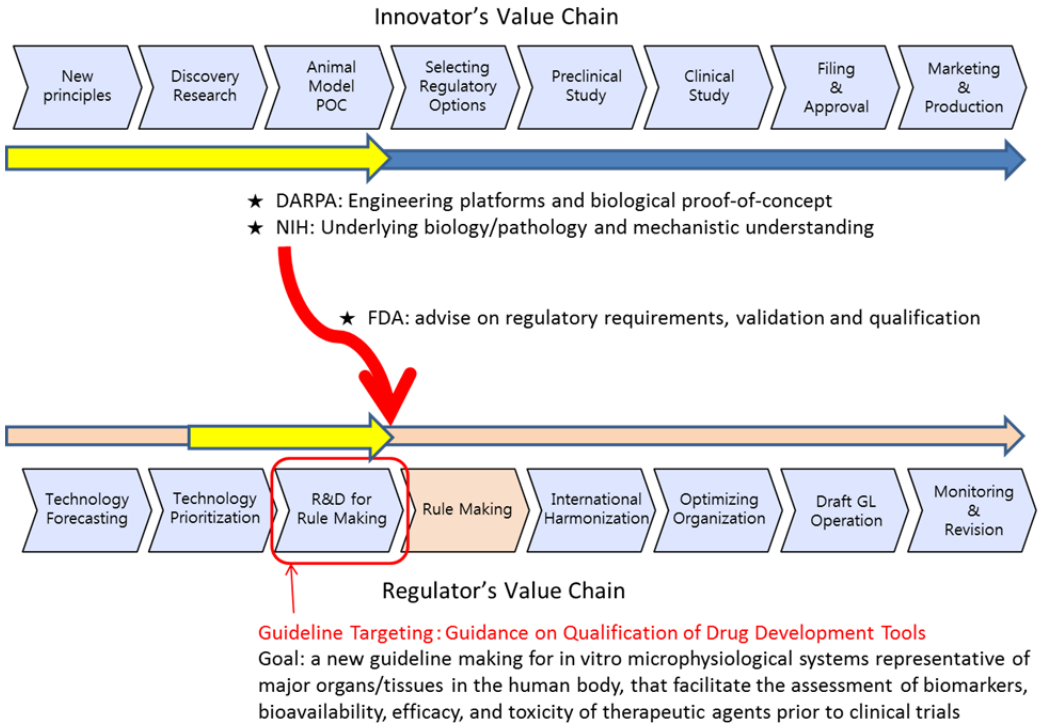


Fig.3 Regulator–Innovator Interaction on Heart-Lung Micromachine for Safety and Efficacy Testing

regulatory approval process through all stages, including research and development and clinical trials, pre- and post-marketing safety, marketing approval, National Health Insurance (NHI) reimbursement price listing, and international deployment. The system promotes research and development using early clinical trial data (Phase I or IIa trials) in Japan and aims at early practical application of innovative medical products having significant efficacy for targeted diseases by conducting priority consultations, prior assessment, and priority reviews under the existing guideline and laws. This fast track system consists of: 1) consistent prioritized consultation with the Japanese Pharmaceuticals and Medical Devices Agency (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) assignment of a manager to assume overall management for the whole process, aiming for approval, including conformity assurance, quality management, safety measures, and review, and 5) strengthening of post-marketing safety measures including the extension of the reexamination period (Fig.4). Regulators in Japan hope the SAKIGAKE approval pathway will cut pharmaceutical review times for clinical trials by half, from an average of two months to one month, and the post-Phase III review time from 12 months to 6 months.

Fig.4, published by the Japanese regulators (MHLW–PMDA) shows the difference between the fast track system and the ordinary regulatory process. The former inserts the consultation and review processes as part of the regulatory process. This inclusion of the consultation processes is quite new and describes precisely what will happen when innovators try to develop products concurrently, and it clarifies the difference between the two regulatory systems in the timeline. Once regulatory processes are changed, the innovator's process also changes, and inevitably, interactions between regulators and innovators are modified. The consultation and review process are interactive in nature, and thus, the newly defined processes are included in both the regulator's process and the innovator's process, as seen in Fig.4. Grey boxes like "Clinical Trials," "Covered by Insurance," and "Commercialization in the Market" are the innovator's processes. Moreover, under the SAKIGAKE Designation System (Fig.4), "Review" indicates that the review and consultation overlap, and that the interactions are more complex. For a better understanding, it would be prudent for stakeholders to separate the innovator's activities from the regulator's activities, as in the RaaP and interactive activities (see Fig.2).

2. Designated Products

The eligibility of the SAKIGAKE designation depends on four specific criteria: a novel mechanism of action, desirability of early commercialization, demonstration of prominent effectiveness, and treatment development and targeting approval in Japan prior to other countries, including global simultaneous submissions. Table 1 lists all products designated under the SAKIGAKE fast track review system until February 2016, namely, six drugs, two devices, two regenerative products, and one virus therapy. The interactions started with the submission for the SAKIGAKE designation, and after the designation is approved, the advantages conferred by the SAKIGAKE system are officially confirmed, and the process continues.

The SAKIGAKE designation system was adopted in 2014 and is yet to reach the final step: "Strengthening post-marketing safety measures." Currently, all the projects are in "Clinical Trail Phase I/II," and the interactions between the regulator and innovators have just started. Thus, we can detect the starting point only. To evaluate the interactions deeply and precisely, we need to follow the activities of both sides as well as the interactions along the five change points of the SAKIGAKE designation, using the improved analytical framework addressing the new regulatory processes and the high resolution of activity separation, as seen in Fig.2.

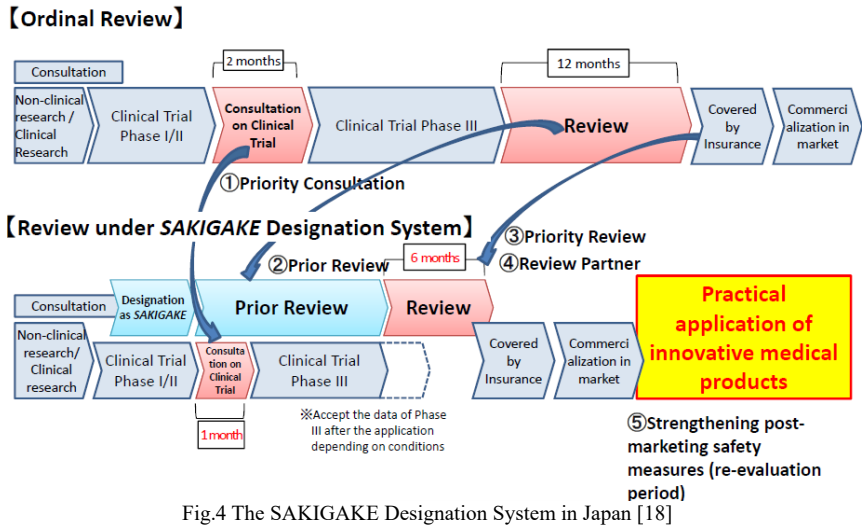


Fig.4 The SAKIGAKE Designation System in Japan [18]

Category	Products	Indication	Company
Drug	ASP2215	First-relapsed or treatment-resistant FLT3 mutation-positive acute myeloid leukaemia	Astellas (Japan)
	Sirolimus (NPC-12G)	Angiofibroma associated with nodular sclerosis	Nobelpharma (Japan)
	S-033188	Influenza A or B virus infection	Shionogi (Japan)
	NS-065/NCNP-01	Duchenne muscular dystrophy	Nippon Shinyaku (Japan)
	BCX7353	Angioedema attacks in patients with hereditary angioedema	Integrated Development Associates (Japan)
	Pembrolizumab (Keytruda)	Unresectable, advanced or recurrent gastric cancer	MSD (US)
Device	Titanium Bridge	Type II thyroplasty	Nobelpharma Co., Ltd.(Japan)
	A liquid adhesion-preventive agent made from trehalose	Postoperative adhesion formation throughout the abdominal cavity after gastrointestinal surgical operations	Otsuka Holdings Co., Ltd.(Japan)
Rgenerative Medicine	Stem cell treatment(STR01)	Spinal cord injuries	Nirpo Corporation (Japan)
	Autologous cardiac stem cells	Heart disease in children.	Japan Regenerative Medicine Co.,LTD (Japan)
Virus Therapy	Reconbinant Herpes simplex virus 4th Generation	Malignant brain tumor	Daiichi Sankyo (Japan)

Table 1 Designated Products under the SAKIGAKE Fast Track System
Source: Ministry of Health, Labour and Welfare (edited by Shingo Kano)

V. CONCLUSION AND POLICY IMPLICATIONS

This paper constructed a framework to analyze the interaction between innovators and regulators in the medical field and applied it to specific cases of collaboration between innovators and regulators in the US and Japan.

In its early phase, the US Heart-Lung Micromachine for Safety and Efficacy Testing project showed that the framework could illustrate the objects of activities ranging from "New Principle" to "Animal Model POC" in the innovator's value chain, as well as "Regulator's Initiative" and "Guideline Targeting" in the interactions. It could also identify the activities that graduate to the next "Rule Making" process in the regulator's value chain. Notably, the designated products are still in the clinical phase, and the process is not complete. However, for the Japanese fast track system in the later phase, the framework analysis provides opportunities to identify improvements to describe the fast track system more precisely through RaaP, and to recognize the problems pertaining to separation of activities into three distinct categories: innovators, regulators, and interactions. These findings relate to a double track framework that puts innovators' activities in parallel with regulators' activities while simultaneously separating them. These two case studies demonstrate the utility of the framework.

The RaaP concept covers the total process pertaining to regulations; thus, we could address the change in the regulatory process, such as the introduction of a fast track system, and we could analyze the total interactions between innovators and regulators. As the HSS concept mainly covers activities "before" rule making and functions as an alerting mechanism for the regulators, RaaP can offer advantages in evaluating how the regulatory process acts on the whole. In the US' case, regulators intend to create new guidelines, and thus, "Guideline Targeting" is essential to bridge both innovators' activities and regulators' activities, to prepare for rule making. Accordingly, a "Guideline of Guideline" like the DDT is needed for the Japanese regulatory system. Japanese regulators should prepare this type of regulatory framework to adopt emerging evaluation technologies. In the Japanese case, we recognize the need for additional future study from the viewpoint of interaction analysis, especially the points of identification for a complex fast track system and how it would work. While this pilot study does not necessarily help us understand the interactions perfectly, it does provide an avenue to analyze regulator–innovator interactions.

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