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The Concept of Regulatory Frontier as a Boundary of Jurisdiction in Medicine

- A Case of Regenerative Medicine in Japan -

Shingo Kano

Graduate School of Frontier Sciences
The University of Tokyo, Bioscience Bldg. #B-17, 5-1-5, Kashiwanoha,
Kashiwa City, Chiba, Japan, 277-8562

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Abstract

A proposed framework using the concept of "Regulatory Frontier" which describes decreasing of capability threshold for making the rules along with the maturation of technology provides a new method to define "Regulatory Space." The Regulatory Frontier could divide regulatory space into "on the rule space" and "off the rule space," and explains why regulation inevitably delays against innovation. When technological development progresses at the point of maturity that needs the rule or regulation for clinical development for medical applications without the rule and the technical standard to utilize it, the technology is in the "off the rule space" and falls into the "regulatory gap." To explain this phenomenon and also discuss the interaction between innovation and regulation, the author introduces a case study of regulatory activities in Japanese regenerative medicine and then theorizes "regulatory gap" and rationalize the alternative path which so called hospital exception with some additional emerging rules in Japan to provide the authorized new therapy to the patients.

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Regulatory Policy Analysis in Medicine : Critical Difficulties

- Many Rules, Technical Standards and Ethics involved
- Case by case : risk based approach in various products & services
- Product Classifications differ between countries
- Elements for policy making are complex and interact each other
- Various stakeholders
- Two departments involved for rule making in Japan (MHLW & METI)

- Lack of effective analytical framework for policy analysis

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Conclusion : A comprehensive framework to solve the difficulties

A New Analytical Framework for Regulatory Space

•A proposed framework introducing the concept of "Regulatory Frontier" which describes decreasing of capability threshold for making the rules along with the maturation of technology provides a new method to define "Regulatory Space"

•The Regulatory Frontier could divide regulatory space into "on the rule space" and "off the rule space," which distinguish whether R&D are supported by regulatory rules and technical standards and explains why regulation inevitably delays against innovation.

•When technological development progresses at the point of maturity that needs the rule or regulation for clinical development for medical applications without the rule and the technical standard to utilize it ("On the Rule Point") , the technology is in the "off the rule space" and falls into the "regulatory gap"

•"Regulation Path" describes how each product progresses against the regulatory situation. It could take a course from "off the rule space" to " on the rule space" and sometimes stay in the off the rule space even after industrialization under the Medical Practitioners Act without any PAL like regulations.

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Background: Existing Concepts of Regulatory Space in Medicine

- Technological Zone: Barry(2006)[1]
  - metrological zones
  - infrastructural zones
  - zones of qualification
- Apply "Technological Zone" to regenerative medicine : Faulker（2009）[2]
- Pre-regulatory space : Hogarth(2012)[3] for Pharmacogenomics
  - Voluntary Genomic Data Submission as a pre-regulatory space
- Biomedical Platform : Cambrosio et al. (2006)[4] for Pharmaceutical
  - Regulatory objectivity targets not only specific instruments or practices and individual representations but also those configurations of practices, instruments, knowledge and clinical expertise known as biomedical platform
- Ongoing, deliberative regulatory space : Wilson-Kovacs and Hauskeller, (2012)[5]
  - the view of regulation as a political process that encompasses on-going deliberations between different stakeholders surrounding decision-making and the symbolic and material power it lends.

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Objectives

- Construct an analytical framework for policy making process and its effect in medical field, that include;
  - define regulatory space
  - describe interaction between innovation and regulation
  - explain rule-out case
  - explain R&D delay without rules
- Conduct case studies using the framework
- First, apply this framework to two Japanese new laws in the regenerative medicine as case studies

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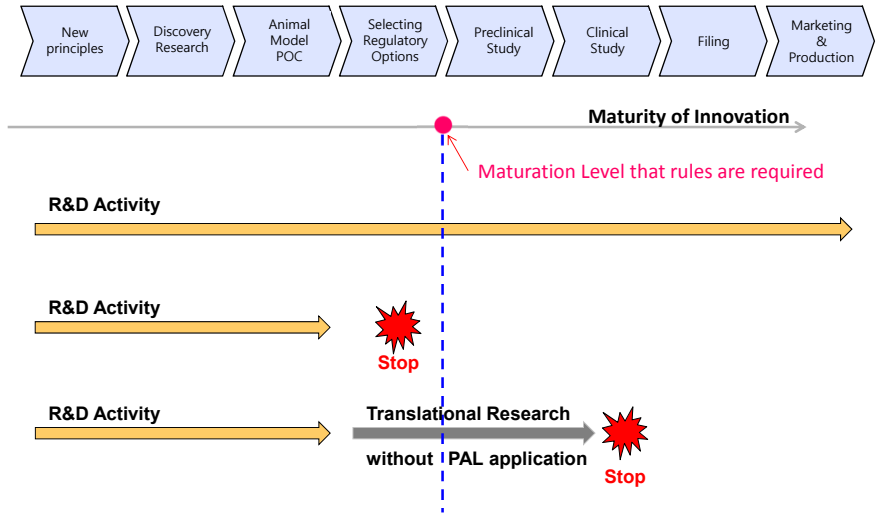
How define Regulatory Space: R & D Process



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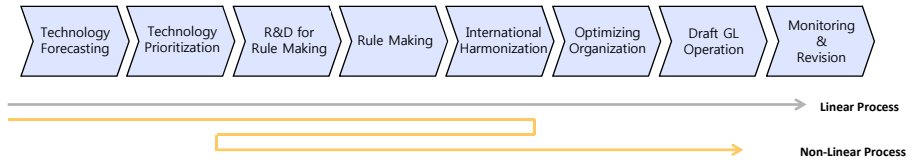
Source) Shingo Kano 2013

How define Regulatory Space: Rule Making Process

Policy Value Chains for Rule Making



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

Source) Shingo Kano 2013

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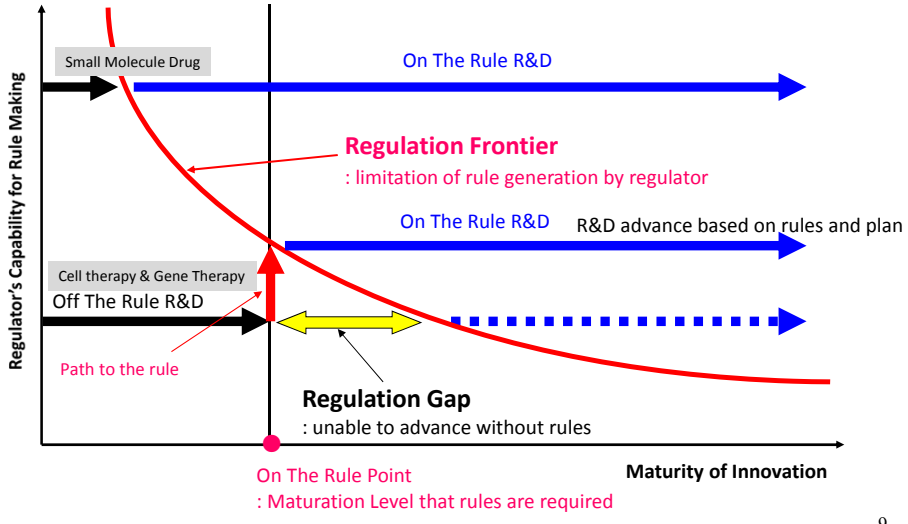
Regulation Frontier & Regulation Gap

Regulation Frontier : limitation of rule generation



Source) Shingo Kano

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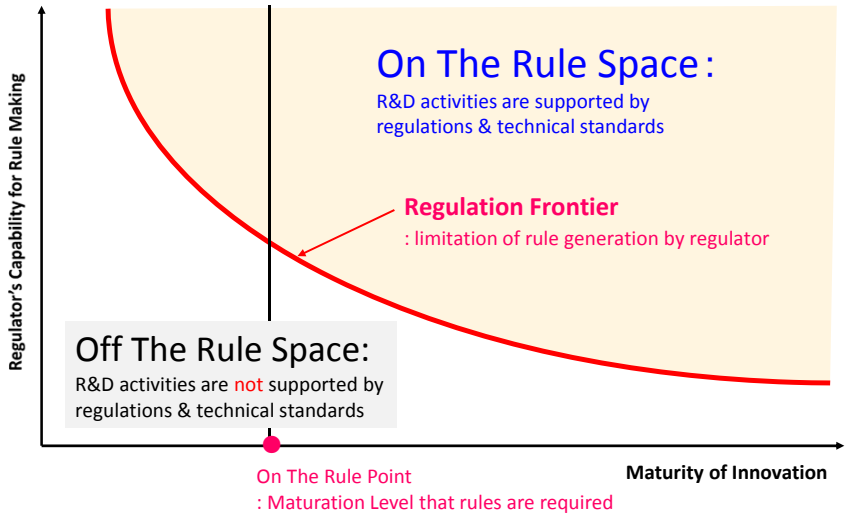
On the rule space & Off the rule space

A new definition of "regulatory space" using Regulation Frontier



Source) Shingo Kano 2013

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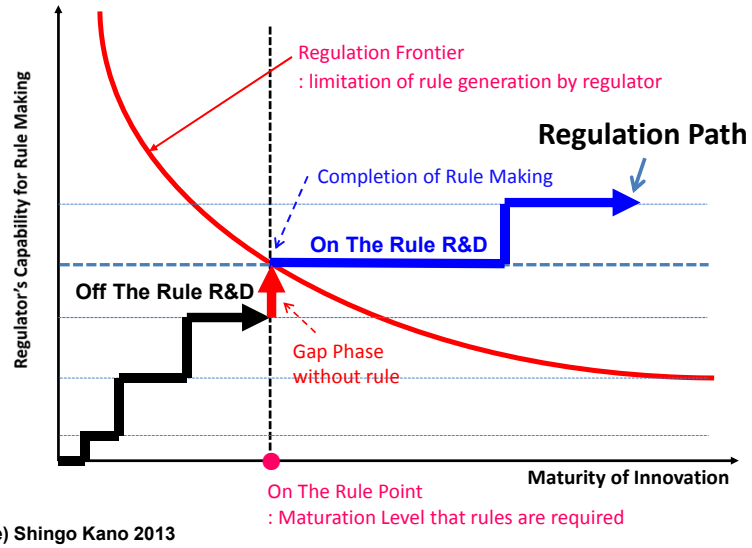
The Concept of Regulation Path

Regulation Path : when and how enter into "On The Rule Space" or not



Source) Shingo Kano 2013

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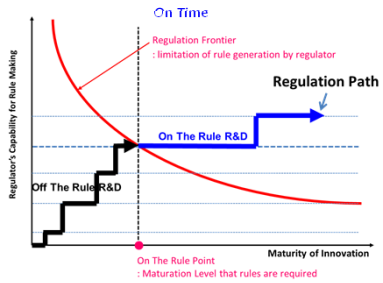
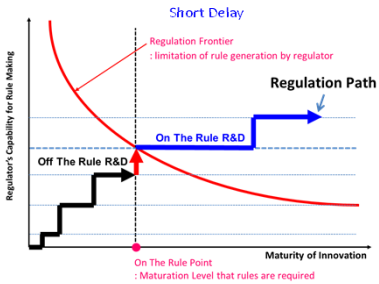
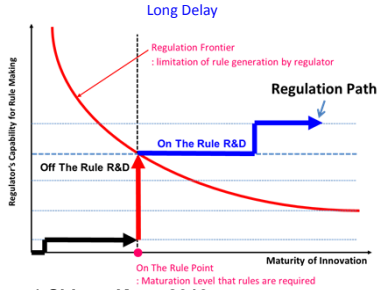
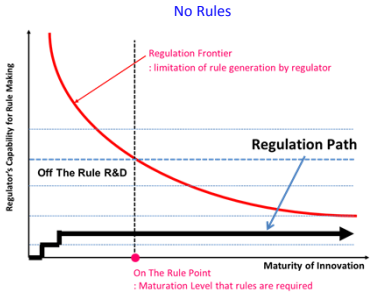
Various Regulation Paths









Source) Shingo Kano 2013

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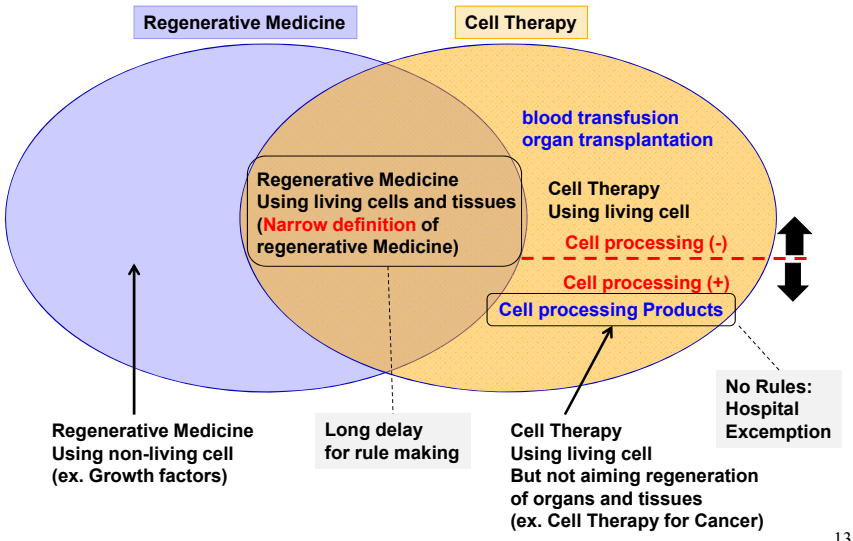
Category of Regenerative Medicine



Source) Yoji Sato, National Institute of Health Science: revised

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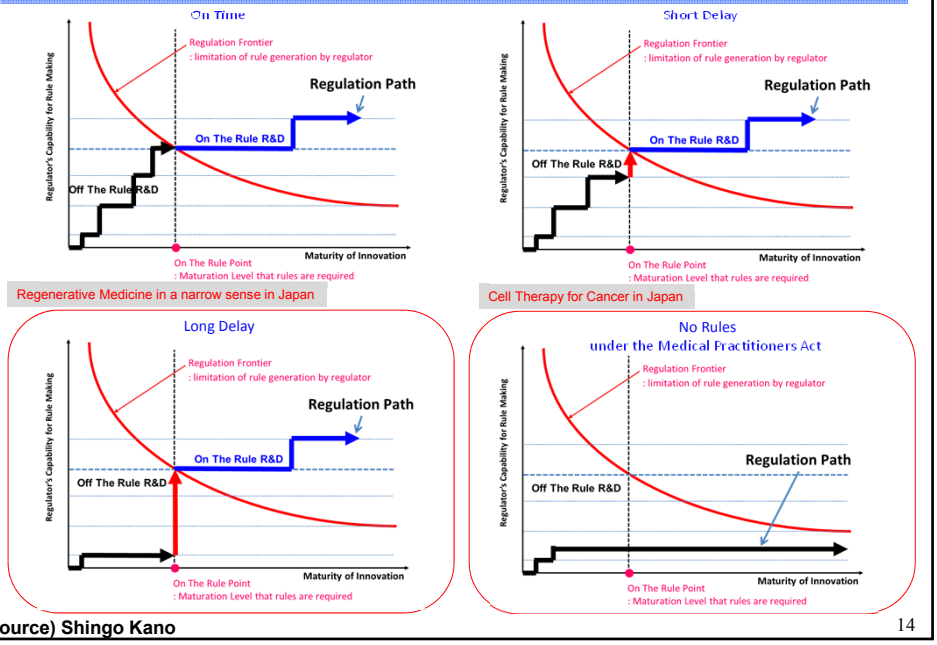
Various Regulation Paths and Two products Situations



Source) Shingo Kano

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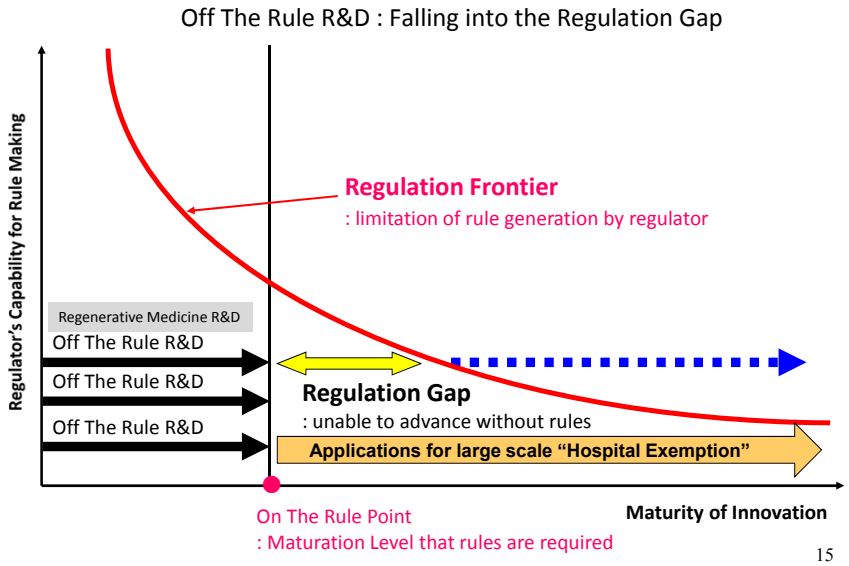
Typical Phenomenon in Regenerative Medicine in Japan



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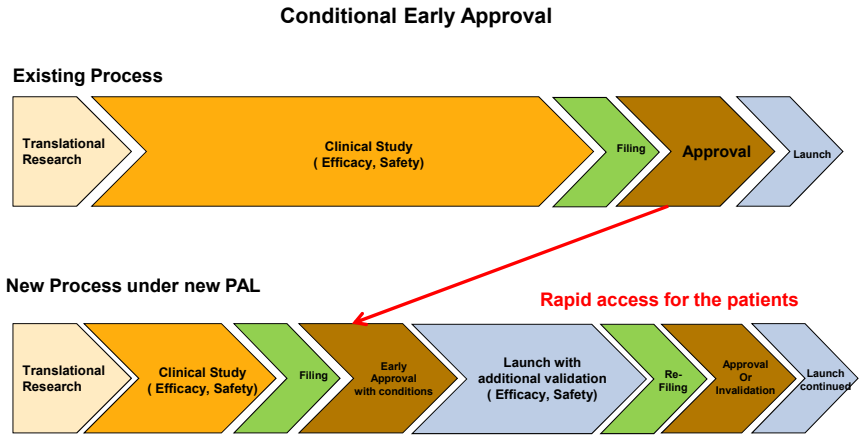
Source) Shingo Kano

The revisions to the Pharmaceutical Affairs Law (new PAL 2013)



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Source) MHLW

Act for the assurance of safety regenerative medicine (ASRM 2013)

ASRM 2013 Summary

The Regenerative Medicine Law sets out the definitions of regenerative medicine and criteria for:

(i) organizations that provide regenerative medicine

(ii) manufacturers of specific cell products, and

(iii) cell culture processing facilities.

With these new rules, Japan intends to expedite the use of regenerative medicine as to ensure the safety of such use.

New Rules Under the Regenerative Medicine Law

The Regenerative Medicine Law categorizes and regulates three types of 'Regenerative Medical Techniques'.

First, before a medical institution provides regenerative medicine to patients for the purpose of treatment, it is required to:

(i) submit a plan for the provision of such regenerative medicine, and

(ii) to meet the criteria regarding the provision of regenerative medicine set out in the Ordinance of the Ministry of Health, Labor and Welfare (MHLW).

Source) Ministry of Health, Labor and Welfare(MHLW)

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Act for the assurance of safety regenerative medicine (ASRM 2013)

The types of regenerative medicine covered by the Regenerative Medicine Law are as follows:

Type	Definitions	Examples
Type I Regenerative Medical Techniques	Regenerative Medical Techniques the effect of which is not clear or which may significantly affect the life or health of human beings even with reasonable care and which is specified in the Ordinance of the MHLW.	Regenerative medicine with induced pluripotent stem cells (iPS cells) or embryonic stem cells (ES cells) products.
Type II Regenerative Medical Techniques	Regenerative Medical Techniques which may affect the life or health of human beings even with reasonable care and which is specified in the Ordinance of MHLW.	Regenerative medicine with own-fat stem cells.
Type III Regenerative Medical Techniques	Regenerative Medical Techniques other than Type I and II Regenerative Medicinal Techniques.	Traditional cancer therapy with activated lymphocyte.

Source) MHLW

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Act for the assurance of safety regenerative medicine (ASRM 2013)

Second, the Regenerative Medicine Law enables medical institutes to outsource processing cell cultures to companies that are not medical institutes. Pursuant to the law, the companies processing cell cultures are subject to the regulation described below.

Types of manufacturers	Cell culture processing manufacturer	Foreign cell culture processing manufacturer	Cell culture processing manufacturer with specific cell culture processing facilities (eg medical institutes)
Required process	Permission	Authorization	Filing
Regulations	• Buildings and equipment used in the cell culture processing facilities must meet the criteria set out in the Ordinance of MHLW. • Cell culture processing facilities must have a staff member who has certain biological knowledge related to the specific cell products. • Manufacturers must comply with the criteria set out in the Ordinance of MHLW related to manufacturing, quality management, testing and inspection, storage, transportation, preparation and maintenance of records and periodical reports.		

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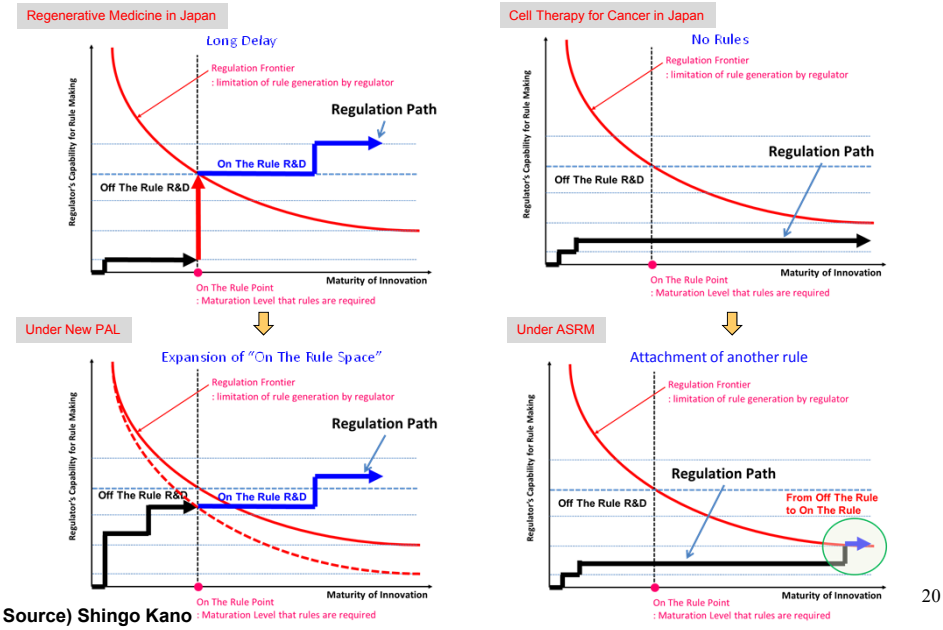
Source) MHLW

Explanations using Regulatory Space & Regulation Path



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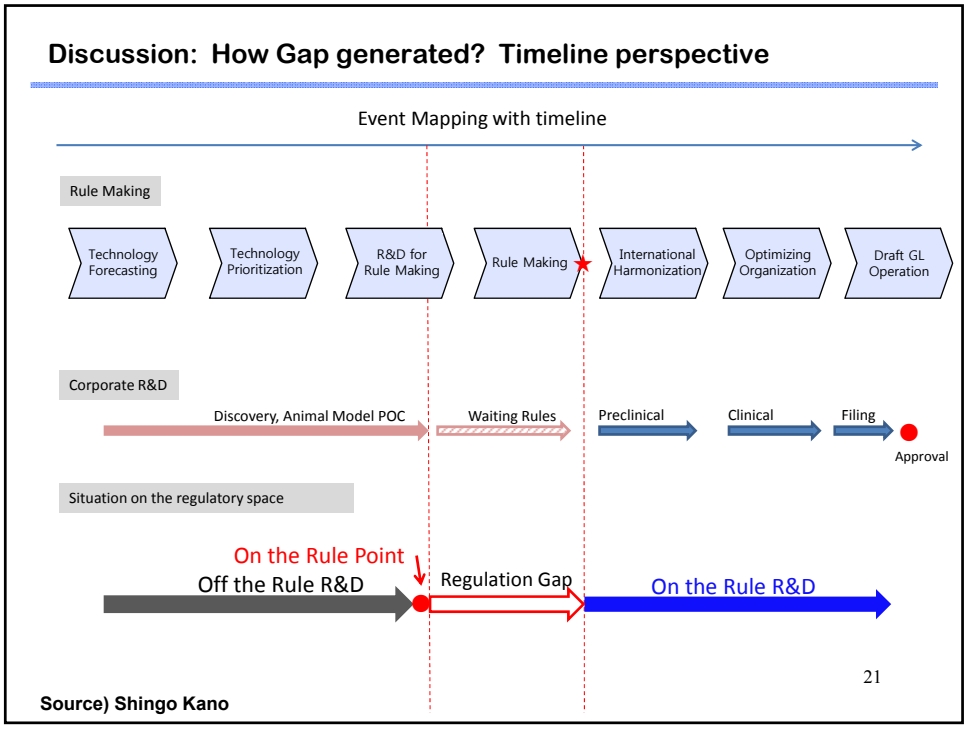
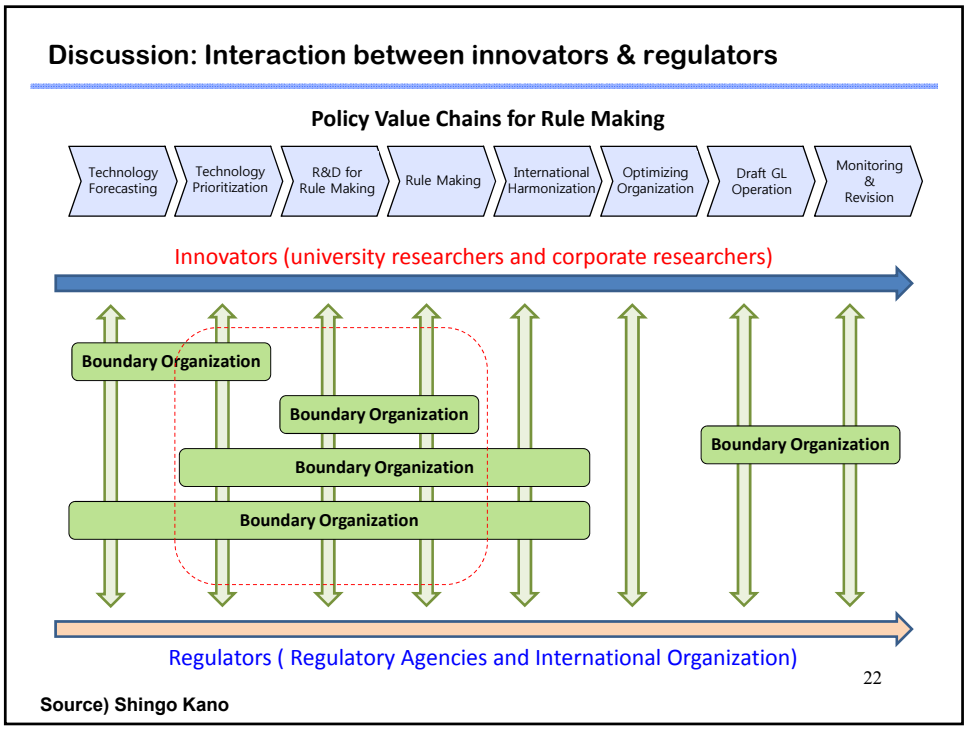
Source) Shingo Kano


Discussion: How Gap generated? Timeline perspective
Event Mapping with timeline
Rule Making
Technology Forecasting
Technology Prioritization
R&D for Rule Making
Rule Making
International Harmonization
Optimizing Organization
Draft GL Operation
Corporate R&D
Discovery, Animal Model POC
Waiting Rules
Preclinical
Clinical
Filing
Approval
Situation on the regulatory space
On the Rule Point
Off the Rule R&D
Regulation Gap
On the Rule R&D
21
Source) Shingo Kano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R&D for Rule Making
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Monitoring & Revision
Innovators (university researchers and corporate researchers)
Boundary Organization
Boundary Organization
Boundary Organization
Boundary Organization
Boundary Organization
Regulators (Regulatory Agencies and International Organization)
22
Source) Shingo Kano

Conclusions:

A New Analytical Framework for Regulatory Space

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Conclusion: (continued)

Lessons from Two Case Studies

•The Goal for policy making is to solve the problematic situation by modifying the regulatory path, regulatory space or both
•Optimal regulatory path is in the course moving into "On the Rule Space"

•New PAL 2013: Conditional Early Approval as an expansion of "on the rule space"
•ASRM 2013 : Attachment of another rule as a bypass for "regulatory path"

Further Research

•Analysis of the role of boundary organization for making the rules as a communication between innovator and regulator
•Utilize the concept of "Regulatory frontier" as a boundary for other products & rules
  – Personalized Medicine / Gene therapy / Medical device
  – Other products other than Medicine, i.e. agriculture, environment, energy…….
•Apply the concept of "Regulatory Gap" and "Regulatory Path" to "chicken and egg" problem in medical product development: which is first, regulatory activity or corporate commitment ?
  – Root A: Breakthrough Innovation -> Regulatory Activity -> Corporate Commitment
  – Root B: Breakthrough Innovation -> Corporate Commitment -> Regulatory Activity

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References:

[1] Barry, A., "Technical Zones," *European Journal of Social Theory*, 9(2), 239-253,

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[4] Cambrosio, A., Keating, P., Schlich, T., and Weisz, G., "Regulatory objectivity and the generation and management of evidence in medicine," *Social science & medicine*, 63 (1), pp. 189-199, 2006.

[5] Wilson-Kovacs D., Hauskeller C., "Cardiac stem cell research: regulation and practice in the UK and Germany," *Innovation: The European Journal of Social Science Research*, 25:4, pp. 409-423, 2012

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