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A Global Conversation
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Comparative Approaches to Biotechnology Regulation

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Conflicts, Biases and Intersecting Activities

No financial interest in, or other ties to, biotechnology companies other than diversified mutual fund retirement accounts

Member, IOM Committee on Ethical and Social Policy Considerations of Novel Techniques for Prevention of Maternal Transmission of Mitochondrial DNA Diseases

Sources:

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Howlett & Migone (2010) "Explaining local variation in agri-food biotechnology policies." Science and Public Policy 37 (10): 781-795 ["H&M"]

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Paarlberg, " Governing the GM crop revolution. Policy choices for developing countries." International Food Policy Research Institute (2000). ["P"]

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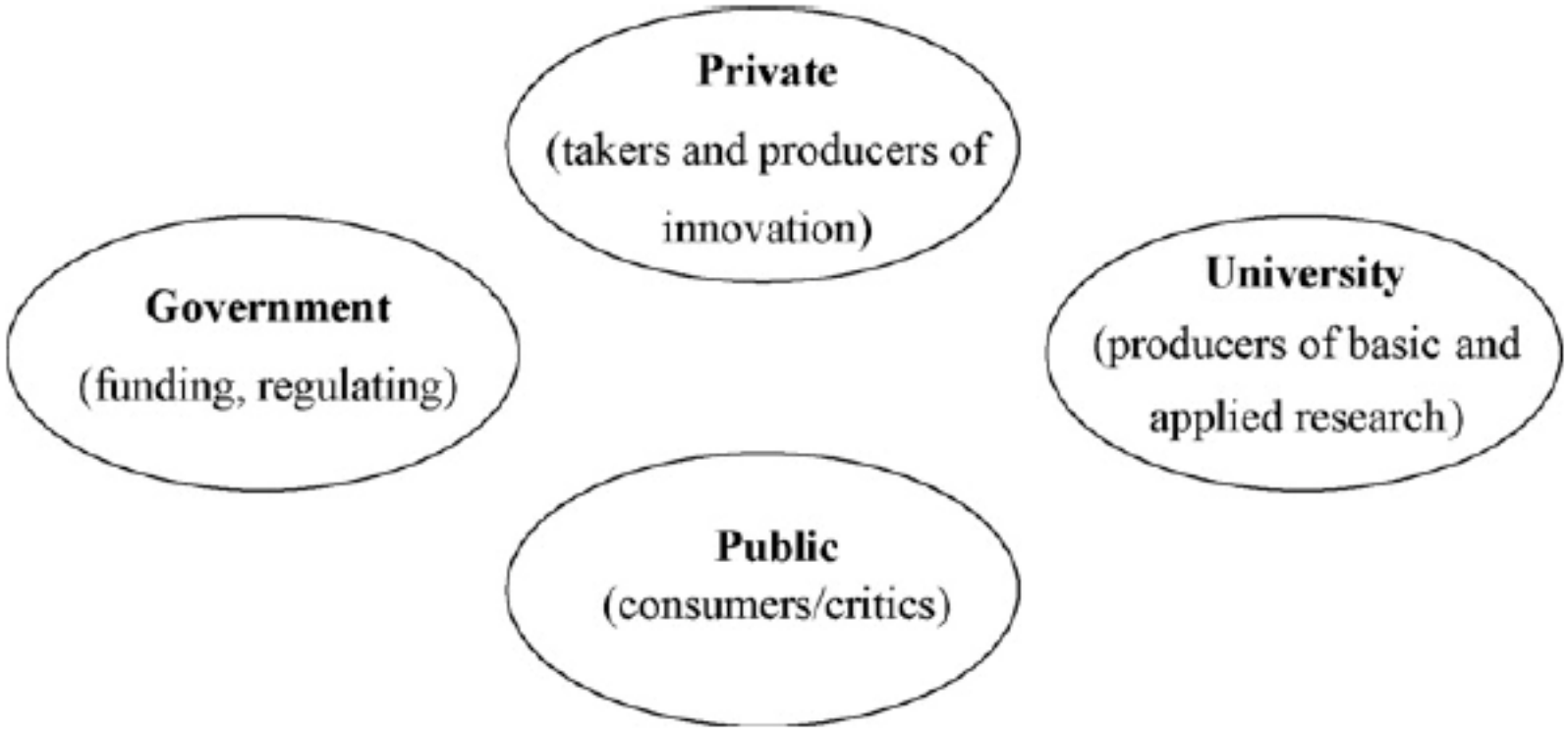

Fig. 1. The basic universe of genomics actors.

Issue Areas	Research issues	Legal issues	Economic issues	Education issues	Acceptance and Implementation issues
Intellectual property rights	-Patent policy	-Intellectual property and licensing practices	-Cost-effectiveness		- Acceptance of private ownership of biotechnology
Public information / Inclusiveness of deliberation	-Ethics review	-Privacy and confidentiality	-IP	-Development of clinical guidelines -Classroom education - Public education -Risk communication	-Behaviour modification in response to genomic results
Retail/Trade	-Patent laws	-Trade agreements	-Market value and pricing -Supply and demand -Commercialization of public-sector initiatives -Creation of new market segments domestically and abroad	-Labelling	-Public adoption of genomic technology
Food and Health safety	-Creation of a regulatory framework	-Regulatory oversight (product and manufacturing review, labelling, laboratory quality and environmental impact)	-Costs related to testing	-Education of health professionals	-Acceptance of the safety of food products by the public
Consumer choice	-Media Advertising	-Genetic discrimination	-Different responses in consumer behaviour	-Information directed towards consumers	-Cultural respect
Public research investment	-Prioritization of research areas (basic, applied and technology development) -Allocation of funds -Provision of the necessary facilities	-Protection of human subjects	-Research and Development funding -Economic incentives for genomics research	-Paedagogical research	-Public Opinion Research

Fig. 5. Haga and Willard list of Biotechnology regulatory issue areas. *Source*: Haga and Willard (2006:967).

Overall Policy Directions

Promotional: support for and removal of obstacles to innovation

Permissive/Neutral/Absent: neither promoting nor hindering biotechnology

Precautionary: slows introduction of new techniques and new product applications

Preventive: entirely defunds or bans the technology or the applications

P/M&H

Table 2. Paarlberg model of policy options and regimes towards GM crops

	Promotional	Permissive	Precautionary	Preventive
IPRs	Full patent protection, plus plant breeders' rights (PBR) under International Convention for the Protection of New Varieties of Plants (UPOV) 1991	PBRs under UPOV 1991	PBRs under UPOV 1978, which preserves farmers' privilege	No IPRs for plants or animals or IPRs on paper that are not enforced
Biosafety	No careful screening, only token screening, or approval based on approvals in other countries	Case-by-case screening primarily for demonstrated risk, depending on intended use of product	Case-by-case screening also for scientific uncertain ties owing to novelty of GM process	No careful case-by-case screening; risk assumed because of GM process
Trade	GM crops promoted to lower commodity production costs and boost exports; no restrictions on imports of GM seeds or plant materials	GM crops neither promoted nor prevented; imports of GM commodities limited in same way as non-GM in accordance with science-based World Trade Organization (WTO) standards	Imports of GM seeds and materials screened or restrained separately and more tightly than non-GM; labeling requirements imposed on import of GM foods or commodities	GM seed and plant imports blocked; GM-free status maintained in hopes of capturing export market premiums
Public information and consumer choice	No regulatory distinction drawn between GM and non-GM foods when either testing or labeling for food safety	Distinction made between GM and non-GM foods on some existing food labels but not so as to require segregation of market channels	Comprehensive positive labeling of all GM foods required and enforced with segregated market channels	GM food sales banned or warning labels that stigmatize GM foods as unsafe to consumers required

Source: Paarlberg, 2000

Governance Implementation Methods

Public Consultation

Voluntary/Self-Regulation

Government Guidelines

Regulatory and Legislative (directed activity or funding preferences)

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Public Consultation

US: National Environmental Policy Act
- deregulation of engineered beets
- approval of genetic construct for engineered salmon

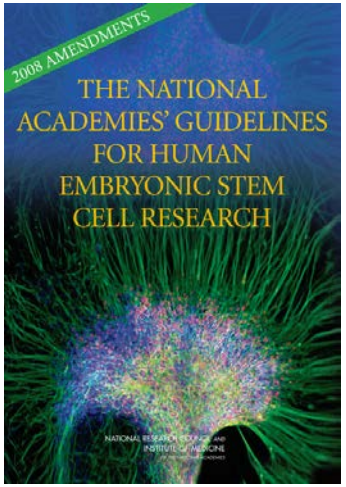
Canada: Royal Commission on New Reproductive Technologies

European Union: Directive on public access to environmental information; applies to GMOs when they may:

☐ Affect and/or interact with biodiversity
☐ Affect other environmental elements (e.g. water, soil, land)
☐ Affect human health and safety through their environmental effects.

Voluntary Self-Regulation

- Asilomar conference
- Guidelines for Human Embryonic Stem Cell Research – National Academies (US); International Society for Stem Cell Research (transnational)
- “Gain of Function” research



Government Guidelines/Guidances

FDA Guidance on Labeling Foods as “Non-GMO”

- not legally enforceable
- strongly persuasive

Council for International Organizations of Medical Sciences (CIOMS) and WHO, “International Ethical Guidelines for Biomedical Research Involving Human Subjects”

- can be more or less restrictive than national law and regulation, e.g. with respect to placebo controls

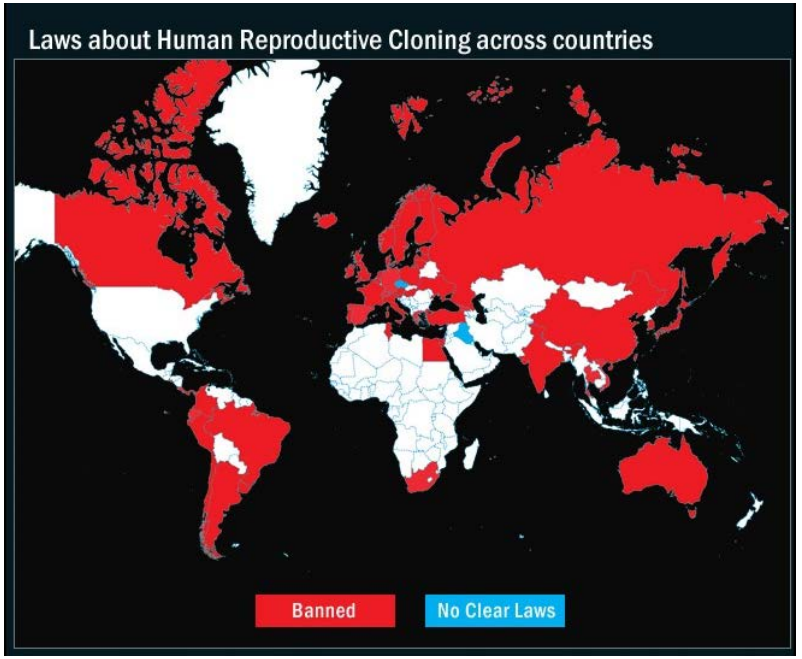
Regulation and Legislation

Legislation setting out overall approaches, creating bureaucratic structures, incorporating limits, etc.

- ex: myriad laws around the world and among many states in US, prohibiting human reproductive cloning

Regulation: Pursuant to legislation, sets out detailed standards and procedures that are legally enforceable

- ex: government conditions on receipt of research grants; technical specifications for facilities; procedures for surveillance, etc.



International Instruments

Council of Europe's *Convention on Human Rights and Biomedicine* (1997) ("Oviedo Convention"):

* Allows use of predictive genetic tests only for medical purposes.

* Allows genetic engineering only for preventive, diagnostic or therapeutic reasons and only where it does not aim to change the genetic make-up of a person's descendants.

* Builds on European Convention on Human Rights and BioMedicine

* In force in, e.g., France, Portugal, Spain

Gene Therapy - United States

- Regulated by Food & Drug Administration
- Subject to the Public Health Service Act (largely focused on purity and potency) and by laws governing drugs and devices
- Strong premarket controls
- Post-market controls weaker (although somewhat stronger since 2007); off-label use a factor
- Review by NIH Recombinant DNA Advisory Committee as adjunct to FDA review
- Human subjects research also covered by local research ethics oversight bodies
- Donors and intermediaries usually permitted to receive compensation

Gene Therapy - Korea

Overall pathway for medicinal products – including biologics – similar to that in the US

Financial burden of trials high for small companies (subjects do not pay for care; sponsor pays for insurance)

Recent emphasis on innovation:

--expanded access to investigational drugs for treatment use or emergency use,

--conditional approval of New Drug Application (NDA),

--risk management plan (RMP), and

--pre-review of application package.

Autologous cell therapy originally not subject to regulatory oversight; now regulated and moved into “conditional approval”

G&S

Gene Therapy - UK

- Operates within context of European Union
- Consistent with EU directives, disfavors payments to donors
- Strong premarket review
- Use of a gene therapy advisory committee for ethics review
- For human germline, Human Fertilisation and Embryology Authority may be implicated
  - offers strong controls over use, as license is needed for both the technology and the facility

REGULATION (EC) No 1394/2007 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 13 November 2007

on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004

(Text with EEA relevance)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European Community, and in particular Article 95 thereof,

Having regard to the proposal from the Commission,

Having regard to the Opinion of the European Economic and Social Committee (1),

After consulting the Committee of the Regions,

Acting in accordance with the procedure laid down in Article 251 of the Treaty (2),

Whereas:

(1) New scientific progress in cellular and molecular biotechnology has led to the development of advanced therapies, such as gene therapy, somatic cell therapy, and tissue engi-

been defined in Annex I to Directive 2001/83/EC, but a legal definition of tissue engineered products remains to be laid down. When products are based on viable cells or tissues, the pharmacological, immunological or metabolic action should be considered as the principal mode of action. It should also be clarified that products which do not meet the definition of a medicinal product, such as products made exclusively of non-viable materials which act primarily by physical means, cannot by definition be advanced therapy medicinal products.

(4) According to Directive 2001/83/EC and the Medical Device Directives the basis for deciding which regulatory regime is applicable to combinations of medicinal products and medical devices is the principal mode of action of the combination product. However, the complexity of combined advanced therapy medicinal products containing viable cells or tissues requires a specific approach. For these products, whatever the role of the medical device, the pharmacological, immunological or metabolic action of these cells or tissues should be considered to be the principal mode of action of the combination product. Such combination products should always be regulated under this Regulation.

EU – Marketing Authorization for an Advanced Therapy Medicinal Product

-- must have a marketing authorisation and is regulated through the centralised authorisation procedure.

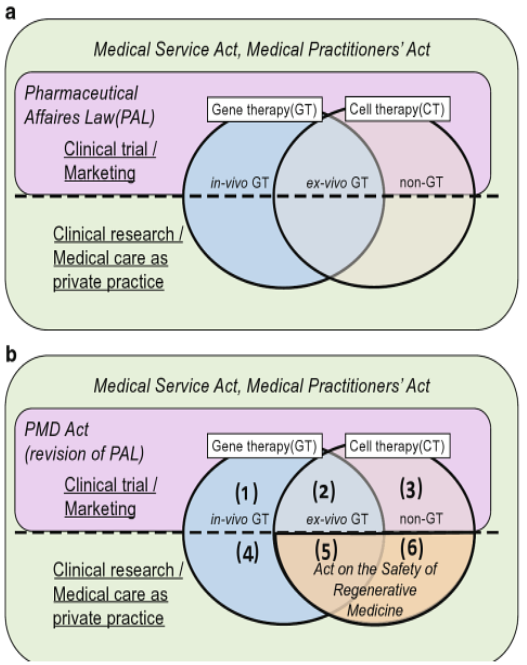
-- the Committee for Advanced Therapies of the European Medicines Agency provides draft opinion on the quality, safety and efficacy.

-- the opinion goes to Committee for Medicinal Products for Human Use for final approval.

Japan

Premarket and Post-Market Controls that Vary Depending on Risk Category *G&S*

D. Maeda et al.



Regulatory Frameworks for Gene and Cell Therapies in Japan 155

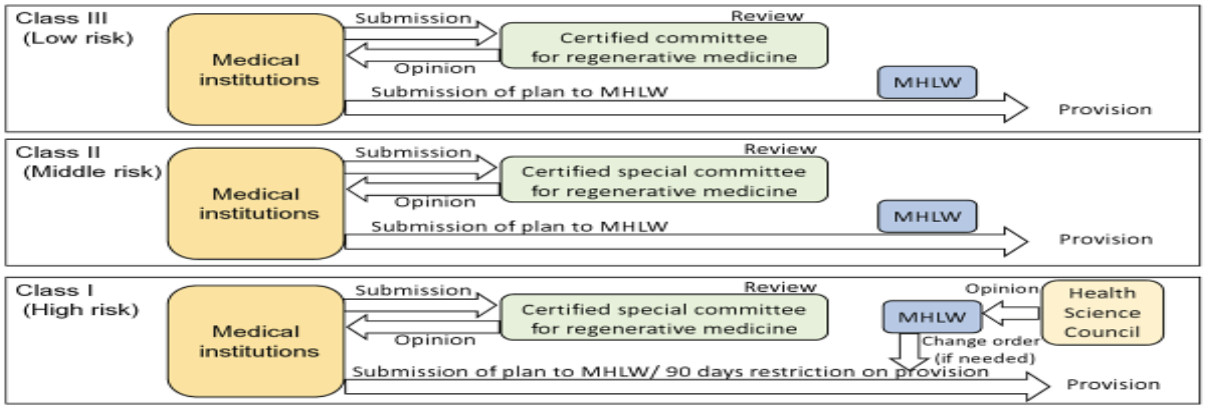


Fig. 3 Procedures to provide regenerative medicine under the new Act in Japan. CT technologies are classified into three categories based on potential risks. The categories are regularly revised based on opinions of the Health Science Council (HSC). Medical institutions which intend to administer CT technologies should submit a provisional plan to the Certified Special Committee for Regenerative Medicine (MHLW certifies the committee) and should then notify MHLW of this plan. In case of Class 1 (high risk) products, MHLW will make a judgment based on the opinions from the HSC within 90 days

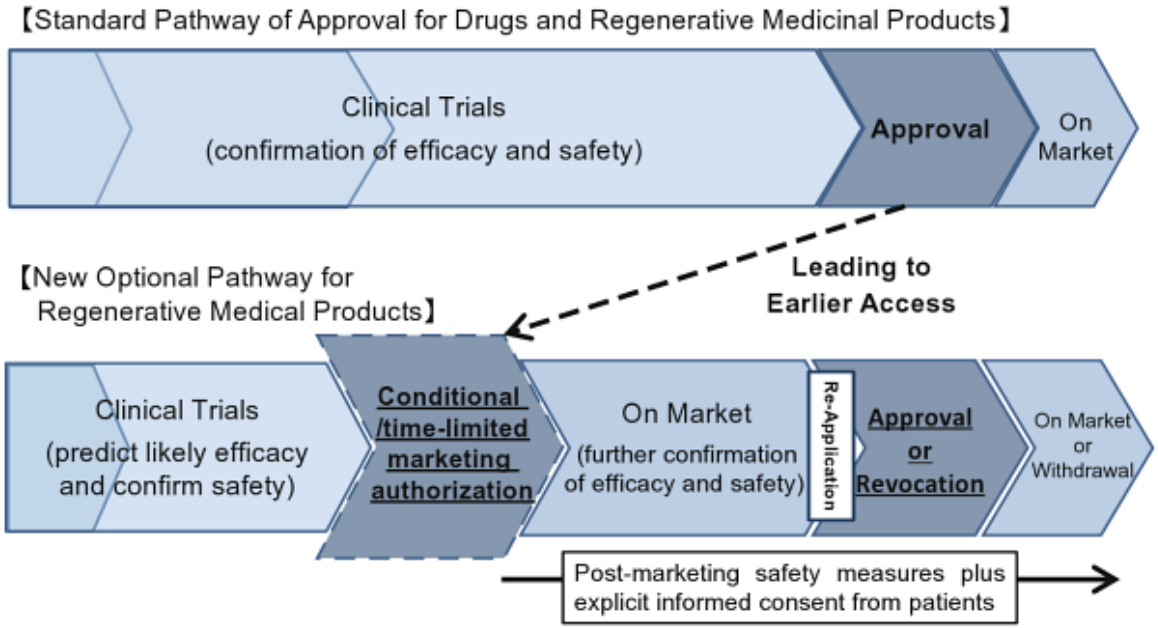


Fig. 5 Expedited approval system under the PMD Act. Under the traditional approval process of pharmaceuticals and medical devices, regenerative medical products must undergo lengthy clinical trials to confirm clinical efficacy before MA. The PMD Act has created a new scheme for regenerative medical products. If the results of clinical trial predict likely efficacy, the product will be given conditional, time-limited MA. Following conditional, time-limited MA, the product is subject to post-marketing safety monitoring in conjunction with surveillance and study to further confirm its efficacy and safety. MAH must submit an application dossier for the second MA. If the product failed to show its expected efficacy, MHLW may revoke its MA

Recently Added in Japan: Conditional Approval Pathway for Regenerative Medicine and Gene Therapy Products

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Singapore

Risk-based tiered approach:

high-risk cell-based and tissue-based therapeutic products are regulated as medicinal products under the Medicines Act.

These include:

*substantially manipulated products,

* products intended for nonhomologous use;

* combined products); and

*gene therapy products

Singapore: Risk Classifications

Table 1 Risk classification for cell- and tissue-based therapeutic products

	Degree of manipulation	Intended use	Combined or use with drug, biologic, or device
High risk	Substantial	Nonhomologous	Yes
	Substantial	Nonhomologous	No
	Substantial	Homologous	Yes
	Substantial	Homologous	No
	Minimal	Nonhomologous	Yes
	Minimal	Nonhomologous	No
	Minimal	Homologous	Yes
Low risk	Minimal	Homologous	No

G&S

Brazil

Legislative and regulatory governance of gene therapy still in development

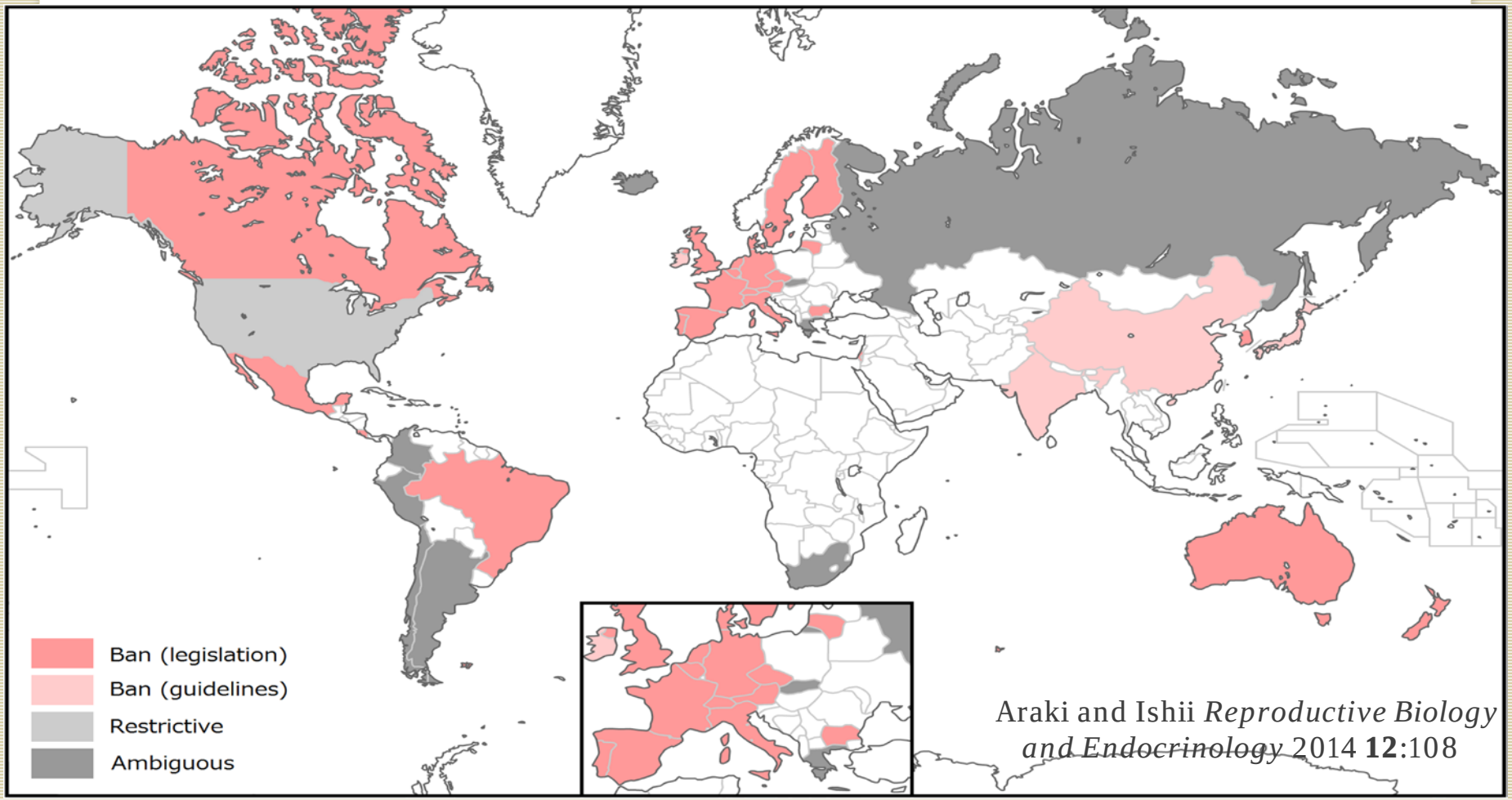
Key elements:

--2005 law related to genetically engineered foods (safety/labeling) and human embryonic stem cell research

--2007 and 2011 regulatory guidances for cell therapy

But: constitutional prohibitions on sale of any kind for human tissue, and a 1996 law prohibiting patenting of human biological materials put the above laws into question

Human germline gene modification regulation. Thirty nine countries were surveyed and categorized as “Ban based on legislation” (25, pink), “Ban based on guidelines” (4, faint pink), “Ambiguous” (9, gray), and “Restrictive” (1, light gray). Non-colored countries were excluded in this survey.



Araki and Ishii *Reproductive Biology and Endocrinology* 2014 **12**:108

A Fundamental Divide

- Regulating the Technology

ex: European Union's Community Strategy for Biotechnology

- easier for public to understand
- focus on key aspects of the underlying science raising questions about predicted effects
- can offer consistent approach to overarching issues, such as human dignity or genetic heritage of humankind
- needs supplemental legislation to focus more closely on specific risks and benefits of specific products or contexts

- Regulating the Products

ex: US Coordinated Framework for the Regulation of Biotechnology

- contextualizes the technology risks and benefits per application
- draws on existing deep expertise and statutory policy choices concerning regulation of various products
- can be confusing to public
- may have unintended conflicts, gaps or redundancies among laws

Some Final Thoughts

Pre-market controls: too weak and adverse events or poor outcomes can slow entire field. ex: Gelsinger case

Premarket controls: too strong and constitutes a barrier to market entry, particularly for start-ups in non-matured fields. ex: AquAdvantage salmon; 'enviro-pig'

Conditions on Grants: can serve as a more flexible regulator almost as potent as most direct regulation. ex: human subjects research

Harmonization: can facilitate cross-border collaboration; reduce redundancies and conflicts in procedures and substantive ethical standards; promote uniformly high standards for research and therapy.
ex: embryonic stem cell research

Innovation ***vs*** Precaution?

Innovation ***and*** Precaution?

Innovation and precaution do not need to be mutually exclusive.

They can be complementary, with public understanding and effective oversight creating the confidence needed to support risk-taking and novel technologies.