POLICY FORUM

REGULATION

Downgrading of regulation in regenerative medicine

What should be a firm commitment to product efficacy is threatened by economic competition

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Science is fundamental to ensuring the safety and demonstrating the efficacy of newly developed medicines. Government agencies play a key role in establishing standards for safety and efficacy. But in a climate of international economic competition, this function comes under frequent scrutiny and pressure. We suggest that in response to this competitive pressure, regulations in some countries have become more permissive. Drawing on controversies over the regulation of regenerative medicine products in Japan and elsewhere, we consider whether the policies that have developed from such tensions can simultaneously protect patients, strengthen health markets, and enhance national competitiveness. These developments shed light on global drivers of a policy phenomenon we call "regulatory brokerage" (*1*). We argue that when regulation does not support the scientific effort to establish the safety and efficacy of medical products, it may be brokered by interest groups, including industry, particular groups of scientists and patients, and policy-makers. In an international context, regulatory changes for short-term economic or political reasons in one country can have a cascading effect, leading to unforeseeable, detrimental consequences for the field of regenerative medicine at the global level.

The field of regenerative medicine may be particularly susceptible to regulatory brokerage because of its economic promise, the huge investment already made in the field, and the hope of relief for growing public health budgets in aging societies. Stem cell–based medicines have always presented a regulatory conundrum because many of the principles used in the standardization, review, characterization, and testing of small-molecule drugs and other chemical entities are of little help in evaluating the use of living cells. But even though standards for product identity, purity, dose, and toxicity may require substantial adjustments to account for the distinct properties of products made from living cells (*2*), the critical feature in which such products should not differ from other drugs is efficacy—the ability to measurably and reliably produce a desired therapeutic effect.

DEGENERATIVE POLICY

Even as countries around the world contend with the problem of direct-to-consumer marketing of unproven stem cell–based interventions by what are seen as "rogue" operators, the field has seen a trend toward loosening the rules for market authorization. This is creating an opaque area of regulatory policy, where it is unclear whether

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deregulation serves competition, science, or patients. South Korea was perhaps the first country to give preferential regulatory treatment to stem cell medicine. In 2011–2012, the Korean Food and Drug Administration issued a flurry of three approvals of the world's first stem cell–based medical products, adding a fourth in 2014. However, only one of the four products is reimbursed by the national health insurance system because of concerns about the strength of efficacy data from premarket trials.

The Korean approvals attracted international skepticism for sacrificing clinical data standards to expedience. But they made a different impact in Japan, which had embarked on a multibillion-dollar initiative to lead the world in regenerative medicine research and commercialization. Japan had already identified the United States as a major competitor in the race to commercialize; Korea's streamlined approval of cell biologics made it a leading contender as well. A 2012 presentation to a Japanese cabinet committee on regulation and regulatory reform highlighted how South Korea had approved five times as many cell biologics as Japan between 2010 and 2012 as an indicator of a purported innovation gap (*3*).

This emphasis on regulatory competition is also reflected in documents of the Research Institute of Economy, Trade and Industry (RIETI), a policy-making organization of the Ministry of Economy, Trade and Industry (METI). The report opens with the observation: "Though Japan has surpassed South Korea in terms of R&D in the area of regenerative medicine, South Korea has been more successful at commercialization" (*4*). The report further cites "tremendous regulatory disparities between Japan and other economies," asserting that "the low number of market approvals is caused by the low number of clinical trials," which the authors attribute to regulatory differences.

In 2013, Japan's government responded to this competitive challenge by amending the Pharmaceutical Affairs Act to create a new category of medicines ("regenerative medicine products") and a review pathway designed to grant such products faster market entry in the form of "conditional approval." These legal changes have drawn both envy and critique from outside Japan. Whereas the Korean approvals represented de facto policy without changes to the legal code, Japan's reforms involved actual changes to law.

The first product to take advantage of Japan's new accelerated pathway was a sheet of skeletal muscle cells intended for use in severe heart failure. Since its 2015 approval, the product has not fared well. The cardiologist who led the small, open-label study that led to its conditional approval subsequently expressed doubts that the product would be adequate to repair severely damaged hearts (*2*). In December 2018, the Health Ministry announced that it would extend the conditional approval period by 3 years because sufficient numbers of patients had not yet been enrolled in postmarket testing (*5*).

Also in December 2018, Japan's drug regulator issued a second conditional approval, for a stem cell biologic for the treatment of spinal cord injury. That decision has also sparked controversy, as it was based on a single, small, uncontrolled, and unpublished study (*6*). In February 2019, the Central Social Insurance Medical Council agreed to reimburse the product at a price of nearly 15 million yen (~$140,000) per treatment course, making it one of the country's most expensive drugs.

DRUG LAG, AN ENDLESS RACE

The perception of regulatory shortcomings or excesses as responsible for national differences in drug approval rates has a long history in the concept of "drug lag." The notion was first introduced in 1973, in a comparison of drug approval times in the United States and the United Kingdom (UK) (*7*). The study's author found the latter country to be faster and suggested that the slower time to decision in the United States harmed both patients and companies. Drug lag soon became a cudgel in the hands of free-market policy organizations, which since the 1970s have embarked on a campaign to weaken the power of the U.S. Food and Drug Administration (FDA).

At the global level, drug lag arguments promote perpetual comparisons between regulatory jurisdictions, in which the regime with faster approvals is often deemed superior to the one favoring a slower, more cautious approach. Solutions proposed by those alleging drug lag almost invariably call for weaker regulation, in the form of easier market entry enabled by faster, and looser, premarket testing. States that fail to relax their health product quality standards risk being accused of bureaucratic sluggishness and obstructionism. Although there is always scope to further refine regulatory codes, sacrificing efficacy requirements for speed is unwise. Unproven and ineffective products can sell well in markets that do not require advance evidence of efficacy (e.g., dietary supplements, homeopathic products). Creating new regulatory carveouts for regenerative medicines is likely to lead to similar outcomes: preemption of adequate treatment, wastage of public funds, and undermining of public trust. Moreover, deregulation in one country may lead international competitors to follow suit.

To our knowledge, the Japanese case is the first instance in which the lowering of market entry standards has been targeted to a medical product on the basis of its material composition. Previous examples of preferential treatment have focused instead on disease severity (e.g., "breakthrough therapy" designation in the United States), incidence (e.g., orphan drug laws), geographical prevalence (e.g., drug development incentive programs for tropical diseases), or mitigation of terrorism (e.g., the FDA Animal Efficacy Rule).

CALLS FOR REGULATORY ROLLBACK

Although Japan's policy experiment has attracted international attention, few are aware that the key principles adopted in Japan's deregulation of regenerative medicine were previously outlined by a free-market policy institute, the Illinois-based Heartland Institute, in the form of a book-length proposal titled *Free to Choose Medicine* (FTCM) (*8*). Although we do not maintain that Heartland Institute is the sole driver behind Japan's regulatory changes, we suggest that it is an important illustration of how attempts by private policy groups in one country may influence lawmaking in another, with consequences that may be disadvantageous to the publics they are intended to serve.

The core concept in FTCM is that clinical trial sponsors should be allowed to begin selling the investigational product to patients while phase 2 studies are still under way. Normally, products must complete a definitive efficacy test in a much larger and more rigorous phase 3 trial prior to sale. This FTCM scheme, which undercuts the need to develop robust evidence of efficacy prior to sale, initially gained little traction at the national level in the United States. Its proponents then began to look farther afield. For example, during the national controversy surrounding so-called "stamina therapy" in Italy, two American scientists and a former FDA commissioner submitted a letter to Italian health authorities, suggesting that Italy could resolve the issue by adopting FTCM. This unsolicited overture, which was immediately rebuffed, prompted a letter of protest from the head of AIFA, the Italian drug regulatory agency, to the then-current FDA commissioner over the attempted interference by U.S. persons in a matter of Italian national interest (*9*).

In Japan, FTCM found more fertile ground. An early version of the proposal was translated into Japanese by the president of the free-market organization Japanese for Tax Reform (*10*), who proceeded to lobby it to members of the Japanese government. The current administration in Japan has

made regulatory reform a core component of its national economic strategy and has made regenerative medicine one of the cornerstones of its medical innovation agenda. This convergence of interests was not missed by key players in the regenerative medicine industry or the policy-making arena.

In 2012, the Japanese Society for Regenerative Medicine began to call for regulatory reforms aimed at accelerating approvals through revisiting clinical testing standards (*11*). By 2013, mentions of FTCM began to appear in presentations made by staff in Japan's drug regulatory agency, the Pharmaceuticals and Medical Devices Agency. The same year, the conditional approvals pathway for regenerative medicine products was introduced. The author of FTCM has since thanked the translator for helping to make his ideas into law in Japan.

GLOBAL IMPACT

One would expect the controversies surrounding the first conditionally approved regenerative medicine products to be a warning to other regulatory jurisdictions. But some regulators have responded to Japan's new regulatory regime as a competitive challenge. In India, the national drug regulatory authority cited the Japanese model in justifying its first conditional approval of a stem cell product in 2015 (*12*). In 2014, a report by the Regenerative Medicine Expert Group convened by the UK government noted Japan's new law as placing the UK at a competitive disadvantage (*13*).

In 2015, a Japanese industry group signed a memorandum of understanding with the Alliance for Regenerative Medicine, a U.S.-based industry organization. By aligning with this international organization, which advocates "clear, predictable, and efficient regulatory and review pathways," Japan gained recognition for its new policies. Numerous joint ventures subsequently sought permission to initiate clinical trials in Japan. In the same year, the California Institute for Regenerative Medicine cited the Japanese system in its annual prospectus, calling for the United States to adopt similar lenient standards (*14*).

In 2016, the Washington, DC–based Bipartisan Policy Center published model legislation that led to the REGROW Act, a bill seeking to allow regenerative medicine products onto the U.S. market upon completion of a phase 2 study—a stage at which robust statistical evidence of efficacy has not been obtained. The group stated that "Europe and Japan have outpaced the United States in modernizing their policies to grant patient access to safe cell therapies." Although the REGROW bill died in committee, months later new language on speeding regenerative medicine approvals was added in an amendment to the 21st Century Cures Act, leading to the introduction of a new FDA regulatory designation for "Regenerative Medicine Advanced Therapies." In January 2019, the FDA projected that by 2025 it would be approving 10 to 20 new cell and gene therapy products per year (for comparison, the FDA had not approved any cell/gene therapy product until December 2017; to date, it still has not approved any stem cell products).

In May 2019, four Republican senators called on the FDA to expand "parallel track" market access for unapproved drugs targeting "critical" diseases (*15*). Their proposal followed a March statement by the Heartland Institute calling for the same measure, which cited Japan's deregulation of regenerative medicine as a successful case. Heartland had previously described FTCM in Japan as "a model for America" (*10*). The push for deregulation, as promoted by FTCM supporters, is beginning to extend beyond stem cells.

The examples above illustrate how sensitivity to international competition can make regulators receptive to lowering regulatory thresholds, without giving sufficient consideration to the long-term effects for patients and health care budgets—and perhaps unaware of the consequences that deregulation can have on a global level. Japan's citizens may be alarmed that stem cell products approved under its relaxed standards are now the subject of widespread skepticism among global scientific communities. Other countries, such as Italy and India, have experienced firsthand how economic agendas, cloaked in the language of serving patients, can undermine standards intended to ensure that new drugs deliver measurable therapeutic benefits. Observers should remain on the alert for policy proposals that seek to accelerate approvals to a speed that makes it impossible to determine whether a product is worth marketing.

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To begin addressing the problem of regulatory brokerage in pursuit of short-term economic advantage, voters and taxpayers need to be informed when public health budgets are spent on medicines that have not undergone sufficient scientific and regulatory review. Patient groups must stay informed and alert to the fact that regulatory permissiveness is often geared as much to expediting profit and prestige for private and state-backed firms as it is to accelerating access. And international science and health organizations must be more proactive in sounding the alarm about how the weakening of regulatory protections can lead to the squandering of public money and erosion of trust in scientific research. ■

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ACKNOWLEDGMENTS

Supported by European Research Council grant 283219 and Economic and Social Science Research Council grant ES/I018107/1.

10.1126/science.aax6184

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Science **365** (6454), 644-646.
DOI: 10.1126/science.aax6184