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***Science* on FDA Liberalization: A Response to the Status Quo Process for Medical Treatments**

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In Japan and elsewhere there have been some moves toward liberalization of the approval of new drugs and treatments. An article in the 16 August 2019 issue of *Science* sounds an alarm against such developments. The authors Douglas Sipp and Margaret Sleeboom-Faulkner deprecate at length the reform proposal of my *Free To Choose Medicine* (hereafter FTCM; see Madden 2018), which served as a model for Japan's legislation authorizing conditional approval for medical treatments focused on regenerative medicine (e.g., stem cells). FTCM enables patients, advised by their doctors, to make informed decisions about early access to new drugs after successful completion of initial safety and efficacy trials. Although Sipp and Sleeboom-Faulkner are on solid ground in recognizing some unscientific use of stem cells via direct-to-consumer marketing, they are, I think, wrong in supposing that Japan's conditional approval will hurt patients by enabling them to gain early access to regenerative medicine treatments. Their judgments are not substantiated by evidence or argumentation about the merits and demerits of the reform; they simply assume that the liberalization is a bad thing. Their article is about 2,900 words in length and appears in *Science*, one of the top-five most cited journals, so it merits a response. I submitted an earlier version of the present article to *Science*, but it was dismissively turned away.

Sipp and Sleeboom-Faulkner give a fair amount of attention to my work and its influence, writing:

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)... 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. (Sipp and Sleeboom-Faulkner 2019, 645)

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, who proceeded to lobby it to members of the Japanese government. (ibid.)

In 2012, the Japanese Society for Regenerative Medicine began to call for regulatory reforms aimed at accelerating approvals through revisiting clinical testing standards. 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. (ibid., 646)

Sipp and Sleeboom-Faulkner do not treat liberal economic reasonings with respect, speaking of such reasoning as subservience to “economic agendas, cloaked in the language of serving patients” (2019, 646), as though I do not sincerely believe that liberalization would significantly benefit humankind. They suggest that the idea of a drug lag is used as “a cudgel in the hands of free-market policy organizations” (ibid., 645).

System goal

Sipp and Sleeboom-Faulkner (2019, 644) believe the goal of government regulators should be ensuring that any drug accessible to patients is safe and effective. Who wants unsafe and ineffective drugs? However, with such a mindset a government regulatory body tends to steadfastly demand ever more testing while giving low priority to opposing views concerned with associated costs. Such costs include the continuation of delays in accessing beneficial new treatments, and higher prices of new drugs, to meet regulatory testing requirements. Our goal should be *better drugs sooner at lower cost*—and that is the subtitle of my book—where the word ‘drugs’ represents all medical treatments requiring regulatory approval. The fundamental issues are not only statistical problems of determining drug efficacy, but also the following: understanding the overall drugs-to-patients system; avoiding procedures that yield unintended and deleterious consequences; and

identifying and removing constraints that impede better drugs sooner at lower cost.

The Food and Drug Administration (FDA) knows that when it approves a drug that subsequently results in unanticipated adverse side effects, especially deaths, it will face negative media attention and, if many people die, Congressional hearings. Such consequences incentivize the FDA toward preserving or even enhancing their clinical testing requirements. What does not make the nightly news, however, is the invisible graveyard of patients dying from not having had access to very expensive, or delayed, or simply non-existent possible new treatments. The FDA has implemented various programs to accelerate the testing of promising drugs by incrementally changing a single regulatory process (Woodcock and LaVange 2007). Notably absent is competition from an alternative access mechanism that may significantly improve the conventional process (Conko and Madden 2013).

Optimal regulatory load

What is the optimal regulatory load for clinical tests and analysis for potential approval of new drugs? Sipp and Sleeboom-Faulkner do not know. No one knows. Nevertheless, Sipp and Sleeboom-Faulkner oppose a FTCM approach that combines informed choice (retaining prescription requirements) and rapid data dissemination and adaptation. Such opposition to liberalization has deep roots. Regulators prefer having simple binary yes/no approval decisions, which exclude the complexities of patient populations comprised of individuals with unique health conditions and unique risk preferences. Sipp and Sleeboom-Faulkner believe that moving away from the so-called gold standard of randomized control trials must necessarily lead to lessening of a firm commitment to product efficacy, but they ignore that sticking to this gold standard is fraught with its own unique ethical concerns (Deaton and Cartwright 2018). Keep in mind that the costs to companies of randomized control trials can have undesirable consequences for how companies select new drug candidates. For example, since cancer survival rates (a key readout for randomized control trials) are far less costly to measure for late-stage cancer patients compared to early-stage cancer patients, all else equal, this motivates companies to allocate resources to late-stage cancer drugs.

To achieve statistical rigor, government regulators responsible for randomized control trials strive for homogeneity of clinical trial patients with minimal concern for the cost of this testing. Such methods do not address the wide diversity of real-world patients as to health characteristics and risk preferences. Moreover, the elimination of choice is justified for today's patients by assuming either that it is necessary for today's patients to join clinical trials in which many do not get

a promising new drug (due to having been assigned to a control group), or that these patients are incapable of making health decisions in their own best interest and therefore choice is not a viable option. Should we not revisit these outdated assumptions, which were the centerpiece of legislation empowering the FDA in 1962 (Grove 2011)?

In contrast, *Free To Choose Medicine* embraces heterogeneous, real-world patients and utilizes rapid technological advancements that continually improve the identification of subsets of patients most likely to favorably respond to a new drug (Khozin et al. 2017). As personalized drugs become increasingly more effective, one can envision ever smaller subsets of patients identified as highly likely to achieve a favorable treatment outcome so that randomized control trials are no longer feasible (Lillie et al. 2011). Such ramifications of personalized drugs spotlight an increasingly significant ethical concern for randomized control trials wherein those patients who are randomly assigned to control groups do not receive the promising new treatment (Stewart et al. 2010), an especially important concern for patients with life-threatening diseases.

A self-adjusting, dynamic system

Sipp and Sleeboom-Faulkner note that the initial stem cell treatments receiving conditional approval and early access in Japan were of questionable value to patients. This is not surprising since conditional approval was in its early startup stage and missing feedback data that helps patients and doctors make informed decisions about the use of early access treatments. Sipp and Sleeboom-Faulkner ignore the long-term benefits to patients and biopharmaceutical researchers from the FTCM focus on rapid posting of treatment results from early access, including patients' health data, genetic data, and relevant biomarkers—all maintained with patient identity kept confidential. The posting of treatment results is the function of FTCM's Tradeoff Evaluation Drug Database (TEDD) which provides the biopharmaceutical industry with a treasure trove of data to spur innovation. Contrast TEDD's open access and real-time availability of data with the status quo process that keeps detailed clinical trial data confidential with only summary data available years after they were generated.

Japan is in the process of implementing their version of TEDD to provide the needed feedback data and move Japan's conditional approval closer to the comprehensive FTCM proposal. Meanwhile, Athersys, a leading company in stem cell science, has partnered with the Japanese company Healios in order to generate clinical trial data in Japan that may lead to conditional approval for an innovative stem cell treatment for heart attacks. Two relevant questions are: For Japanese

citizens, how important is early access to an innovative alternative to standard treatments for heart attacks? Assuming this stem cell treatment is granted conditional approval, what will likely be the experience for Japanese patients who voluntarily choose early access?

As to importance, ischemic stroke is a leading cause of disability and mortality worldwide, especially so in Japan with its aging population. The approved treatments, tissue plasminogen activator and mechanical thrombectomy, need to be administered quickly, unlike the 36-hour window for Athersys's Multistem therapy.

Japan's conditional (FTCM) process involves a fundamental tradeoff that impacts the patient experience. The patient, in consultation with doctors, may opt to forgo the standard assessment of safety and efficacy based on randomized control trial data. The patient has the freedom to choose new drugs five to seven years earlier than waiting for the standard approval process. This becomes more important in an environment of fast-paced innovation. The FTCM focus is on observational (real-world) data and the freedom of patients, advised by their doctors, to decide on one of three choices: (1) standard approval drug, (2) conditional approval drug based on TEDD data currently available, or (3) waiting for additional TEDD data before making a decision. Such liberalization promotes greater drug development. For any possible drug, the issue is not merely one of how long it takes to get it to patients but whether it even comes into existence.

No one knows the optimal level of regulation, especially in a world of fast-paced innovation. Is it not advantageous to allow patients, in consultation with doctors, to make an informed decision? If the Multistem treatment gains conditional approval, expect usage of the treatment to accelerate if early treatment results are superior to standard treatments and vice versa. This constitutes a dynamic, self-adjusting system. With favorable results, thousands of patients will generate both treatment results and patient-specific data enabling subsets of patients to be identified who either do exceptionally well or experience an unfavorable outcome. This better equips patients to make an informed choice based on real-world data whose utility increases with thousands of observations, far greater than the number of patients in a typical randomized control trial.

Sipp and Sleeboom-Faulkner assert that "sacrificing efficacy requirements for speed is unwise" (2019, 645). How do they know that? Apparently, this assertion is due to their skepticism about the ability of patients and doctors, even with access to TEDD information and likely private-sector products to assist the evaluation process, to discern the 'good' not-yet-fully-tested drugs from the 'bad.' This is an empirical issue. Japan's forthcoming implementation of their version of TEDD will enable a test of whether the Japanese experience with conditional approval more closely resembles the dynamic, self-adjusting system that benefits

patients, as outlined above, or a chaotic environment with patients and doctors making decisions that fail to provide patient benefits and thus supporting Sipp and Sleeboom-Faulkner's skepticism (Hudgins 2018).

Innovation and resource allocation

Sipp and Sleeboom-Faulkner ignore the role of drug development in the overall drugs-to-patients system. The 'better drugs' part of the goal of *better drugs sooner at lower cost* is driven by the speed and effectiveness of a society's innovation process for developing new drugs. One key driver is rapid dissemination of new data so that scientists throughout the biopharmaceutical industry and other research organizations quickly gain insights leading to new and fruitful hypotheses. Again, the publicly available TEDD data will be a treasure trove for scientists seeking a better cause-and-effect understanding to undergird the development of more and better drugs.

Another key driver is resource allocation. Imagine a world where resources automatically flowed to the most highly skilled scientists, including those with ideas that substantially differ from the existing paradigm of cause-and-effect logic for a particular target disease. Ideal, yes; but this is not today's world. For biopharmaceutical companies, including startup companies, capital is allocated based on risk-adjusted return on investment. The larger the regulatory costs, delays, and uncertainties, the lower is in large part the anticipated return on investment. With FTCM, new drug revenues can begin five to seven years earlier versus the standard approval process, and with far less expenditures for regulatory costs. Expect substantially more capital invested in drug development due to FTCM, plus heightened competition among companies participating in early access programs. Consider a startup company with exceptionally skilled scientists and a potential breakthrough drug that entails fundamental new thinking, but that is in need of capital funding. Because of its unconventional approach relative to existing FDA-tested drugs for treating the targeted disease, venture capitalists will view future FDA clinical evaluation criteria for late-stage randomized control trials to be difficult to forecast and possibly excessively stringent. Hence the risk for providers of capital will be high. In contrast, such risk is reduced in a FTCM world where drug effectiveness is more swiftly ascertained with real-world data. In this environment, expect more capital to flow to startup companies with new thinking and high scientific skill.

In opposing liberalization, Sipp and Sleeboom-Faulkner suggest that the conventional randomized control trial approach coupled to incremental changes is beyond criticism. It is not. Their article is neither based on logical argument

nor evidence. I think their judgments are irresponsible, and when such judgments appear in an influential journal like *Science*, we must do what we can to bring greater accountability and responsibility to the discussion.

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