PERSPECTIVE

Japan's Drug Regulation During the COVID-19 Pandemic: Lessons From a Case Study of Favipiravir

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During the coronavirus disease 2019 (COVID-19) pandemic, the balance between social pressure for rapid drug development and time-consuming scientific evaluation of drugs became a major social issue. In Japan, although favipiravir was championed by mass media and politicians as a promising drug for COVID-19 treatment, the Japanese regulatory authorities did not grant approval based on the phase III trial (Table 1). Through the case study of favipiravir, importance of robust scientific evaluation of efficacy prior to drug approval was discussed.

The significant socio-economic impact of the COVID-19 pandemic has highlighted the challenges for development of novel therapeutic agents and vaccines for the regulatory bodies worldwide. For example, in May 2020, the US Food and Drug Administration (FDA) granted an Emergency Use Authorization (EUA) for a therapeutic drug, remdesivir, based on the interim results of a phase III trial. In addition, Operation Warp Speed by the US government and similar initiatives for vaccine research in other countries have succeeded in the unprecedentedly rapid development and approval of several vaccines against COVID-19 by December 2020.

On the other hand, there have been many candidate drugs that were initially assumed to be promising but were eventually proved to be ineffective in clinical trials. Notably, after ex-President Trump repeatedly touted an antimalarial drug hydroxychloroquine as a "game changer," the FDA issued a letter granting an EUA in March despite weak evidence of efficacy.[1] By early June, however, virtually every published study reported that the drug was not effective in reducing either mortality or morbidity, resulting in the FDA's revocation of hydroxychloroquine EUA on June 15, 2020.

Thus, under the COVID-19 pandemic, the balance between the social pressure for rapid drug and vaccine development and the time-consuming scientific evaluation of clinical trials becomes a major social issue globally. The situation is the same in Japan. Favipiravir (Avigan) developed by Fujifilm Toyama Chemical has been highly anticipated as a new drug for COVID-19 treatment in Japan, especially because it is a domestically developed product. Beginning in the spring of 2020, it was widely covered by the mass media, such as television programs and newspapers, as a breakthrough new drug. Furthermore, the former Prime Minister, Shinzo Abe, announced that the drug would be given approval for COVID-19 treatment by May 2020, before the completion of a phase III trial. However, Japan's regulatory authority did not adopt his policy and revealed in December that the efficacy of favipiravir could not be confirmed based on the phase III trial.[2] Such upheavals concerning favipiravir provide several insights surrounding drug regulation and regulatory science of Japan and beyond.

Favipiravir is a competitive inhibitor of RNA-dependent RNA polymerase, preventing viral transcription and replication, and was first approved in Japan in 2014 for treatment of novel or re-emerging pandemic influenza virus infections (limited to cases in which other influenza antiviral drugs are ineffective). The phase III trial submitted for the regulatory approval at that time was a double-blind randomized controlled trial (RCT) designed to show noninferiority to oseltamivir for treatment of influenza.[3] However, it failed to show noninferiority, but rather showed a statistically significant increase in illness time in the favipiravir group (hazard ratio: 0.818, 95% confidence interval: 0.707–0.948, noninferiority margin: 0.784). Therefore, Japan's regulatory authority, Pharmaceuticals and Medical Devices Agency (PMDA), officially concluded that the efficacy of favipiravir was not demonstrated. In addition, in terms of safety, the teratogenicity of the drug shown in animal

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Table 1 Timeline of events and available data of favipiravir for COVID-19 in Japan

Date	Events	Available Data
March 2014	Favipiravir obtained regulatory approval for treatment of novel or reemerging influenza	
March 2020	Fujifilm began a randomized, placebo-controlled, single-blind phase III clinical trial for treatment of COVID-19 in Japan	*In vitro* efficacy was suggested
May 2020	Then Prime Minister, Shinzo Abe, announced that favipiravir would be given approval for COVID-19 treatment by May 2020	Preliminary clinical studies, anecdotal case series and interim analysis of an observational study were reported
July 2020		Final analysis of an observational study and an open-label RCT in Japan was reported
September 2020	Favipiravir met the primary end point in phase III clinical trial in Japan	Japan's domestic single-blind RCT was reported
October 2020	Fujifilm submitted new drug application for favipiravir as COVID-19 treatment in Japan	
December 2020	The PAFSC concluded that the approval should not be granted and that continued review was necessary	
Within the first half of 2021	The interim analysis of the phase III pivotal study in the US (PRESCO study) is scheduled.	

COVID-19, coronavirus disease 2019; PAFSC, Pharmaceutical Affairs and Food Sanitation Council; RCT, randomized controlled trial.

experiments was considered as a major issue. Interestingly, however, given that highly pathogenic influenza virus infections can be a menace to society, the drug was approved in order to contribute to the preparedness against them, and under the condition that it would not be manufactured unless requested by the Minister of Health, Labor, and Welfare (MHLW) of Japan.

However, in March 2020, after declaration of the COVID-19 pandemic, several clinical trials of favipiravir were launched in Japan based on the observed *in vitro* efficacy against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Of note, even before the results of clinical trials were available, the drug was widely covered by the mass media as a promising therapeutic agent, and social and political pressure increased for early approval before the appearance of scientifically verified results. However, the PMDA and MHLW adopted a regulatory standard similar to that of a conventional new drug application (NDA), requiring the results of RCTs rather than exploratory trials.

Consequently, despite the former Prime Minister's appeal in May, the NDA of favipiravir was not submitted until October 2020, when the results of the phase III study were finalized. The study design was a placebo-controlled, single-blinded RCT for 156 Japanese patients with COVID-19 with nonsevere pneumonia.[4] The primary end point was time to negative conversion of detectable SARS-CoV-2 viral RNA in the reverse-transcriptase-polymerase chain reaction assays, and to alleviation of symptoms (body temperature, oxygen saturation, and chest images). The results were 11.9 days for the favipiravir group and 14.7 days for the placebo group ($P = 0.0136$).

The submitted data and PMDA's review report were discussed in December 2020, by the Pharmaceutical Affairs and Food Sanitation Council (PAFSC), but it concluded that the regulatory approval should not be granted for at that time and that continued review was necessary. The main problem was that the study was single-blinded, despite the fact that the primary end point was a so-called soft end point, including symptom relief and arbitrary assessment schedules. The reviewers found that the biases between the two groups were too problematic to confirm its efficacy, even though Fujifilm insisted that the study design was agreed upon with the authorities before the study inception. In any case, it was officially decided that the advisability of approval would be determined based on the forthcoming results of ongoing clinical trials conducted in Kuwait and the United States, as there was insufficient data from the domestic clinical trials alone.

However, Dr. Reddy's Laboratories, a company involved in the two overseas trials outside Japan, announced on January 27, 2021, that it terminated the double-blind phase III trial in Kuwait.[5] This was because an interim analysis of this trial, involving 353 patients hospitalized with moderate to severe COVID-19 , did not show a statistically significant difference for the primary end point (i.e., time to sustained hypoxia resolution) between favipiravir and placebo (7 vs. 8 days, $P > 0.05$). Meanwhile, the company stated that it will continue the phase III pivotal study (PRESCO study) for patients with COVID-19 with mild to moderate symptoms in the United States, with the goal of alleviating symptoms and preventing disease progression. The PRESCO study is planned to include 826 patients, and drug administration of patients has begun since December 2, 2020, with an interim analysis scheduled within the first half of 2021.[6]

The above-mentioned series of events surrounding favipiravir has revealed three issues regarding drug regulation in Japan; first, the pharmaceutical industry as well as the medical society insufficiently recognize the importance of conducting a study with a scientifically appropriate design, which should be underscored even in the emergency situation of the COVID-19 pandemic. The Japanese phase III trial included a relatively small number of cases and was single-blinded with a soft end point, presumably aiming to be conducted

and evaluated at a lower cost in a shorter period of time compared with robust double-blind trials, as are the cases with the phase III studies in the United States and Kuwait. Although it is commendable that the PMDA's reviewers correctly pointed out the presumed biases by the participated investigators who already knew the allocated treatment arm, it is unfortunate that a basic principle of phase III clinical trials was not fully recognized to minimize biases among the stakeholders.

Meanwhile, the efficacy of remdesivir and dexamethasone was shown in clinical trials following this principle. The phase III study of remdesivir was double-blinded with 6,425 patients and a soft end point (i.e., time to recovery), whereas the dexamethasone trial was an open-label trial with 1,062 patients and a hard end point (i.e., all-cause mortality).[7,8] Therefore, it is reasonable that both drugs were approved for the treatment of COVID-19 in Japan and other countries. After all, it was reported on February 2021, that Fujifilm was considering relaunching a double-blind, placebo-controlled RCT of favipiravir in Japan.[9]

Second, the harm of the occasionally ambiguous and incoherent criteria for approval in Japan became apparent. In the regulatory review of favipiravir for COVID-19, priority was rightly given to scientific assessment over social and political pressures. However, at the time of the initial approval in 2014, even though the efficacy of the drug against influenza had not been scientifically proven, it was approved considering the social conditions for a novel or re-emerging pandemic influenza preparedness. One of the reasons why Fujifilm conducted such an inadequately designed domestic phase III trial for COVID-19 is very likely that they expected that, as was in the previous case, the review for approval would be lenient in an emergency situation under the COVID-19 pandemic.

Third, the regulatory process lacks adequate transparency of information. Despite the nationwide interest for the regulatory review for favipiravir, the PMDA's review report has not been made public, and the published minutes of the PAFSC meeting are mostly blacked out.[10] Furthermore, as of February 2021, neither the phase III study of favipiravir for influenza in 2014 nor the recent phase III study for COVID-19 that ended on September 2020, have been academically published, although proactive information disclosure, such as preprint publications, are on the rise during the COVID-19 pandemic. This makes the reasoning behind the regulatory decisions unclear and hinders evaluation by third parties, leading to distrust against the regulatory authority.

The series of events surrounding favipiravir reminds us that planning rational clinical trials and performing robust scientific evaluation of efficacy and safety through consistent and transparent regulatory process are essential before approval and cannot be omitted. In addition, the mass media and politicians need to ensure that their coverages and statements are based on scientific evidence, and should not prematurely distort information on unverified new drugs as if they are effective treatments. Those lessons would be also true for every country in the context of the need for urgent drug development to contain the COVID-19 pandemic.

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AUTHOR CONTRIBUTIONS
All the authors contributed equally to this work.

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