Japan's Special Approval for Emergency System During the COVID-19 Pandemic

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The development of drugs for coronavirus disease 2019 (COVID-19) is a global challenge. In Japan, remdesivir was approved in May 2020 for COVID-19 caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. In February 2021, a vaccine against COVID-19 was approved. These two approvals were made using the Special Approval for Emergency system in Japan. This Japanese system was started in 2010 and has been used to approve four drugs to date, including remdesivir and the Pfizer COVID-19 vaccine. This paper discusses future challenges for Japan's Special Approval for Emergency system and organizes what can be learned from experiences to date. As a result, I would like to point Out the following issues. (i) Special Approval for Emergency is a system for approving drugs approved overseas, not a system for approving drugs originally developed in Japan. A system to approve drugs that have not been approved in foreign countries needs to be considered. (ii) In the Special Approval for Emergency system, it is necessary to ensure that postmarketing activities are conducted in accordance with the Risk Management Plan and the conditions of approval, to disclose the results in a timely and speedy manner, and to judge the appropriateness of continued approval based on the results of postmarketing activities.

On May 7, 2020, the Ministry of Health, Labour, and Welfare (MHLW) in Japan granted Special Approval for Emergency (SAFE) to remdesivir, an antiviral agent of nucleotide analogue prodrug, developed by Gilead Sciences, indicated for coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.[1] The approval of remdesivir in Japan was only one week after the granting of the US Emergency Use Authorization; submission of the application was on May 4, 2020, and the review period was only 3 days. The new drug application data package for remdesivir consisted almost totally of clinical trial results conducted in foreign countries. On February 14, 2021, the MHLW also granted SAFE to tozinameran (Comirnaty), a new vaccine against COVID-19 developed by Pfizer and BioNTech. Vaccination against COVID-19 was started in Japan on February 17. Pfizer submitted a new drug application to the MHLW on December 18, 2020. This vaccine is a messenger RNA vaccine with a completely new and innovative mechanism of action. Clinical development required about 8 months, then 58 days of the review was required for tozinameran.[2] These two cases represent unprecedentedly fast approvals in Japan. A system called "Special Approval for Emergency" (SAFE) was used for this review. The SAFE system is for emergency situations and shortens the approval process in Japan for drugs already in use overseas. In the case of the MHLW, it evaluated data from a large-scale international phase II/III study and a small amount of Japanese population data submitted by Pfizer. The overseas data consisted of efficacy and safety data from about 43,000 patients,[3] while the Japanese data were from a phase I/II trial that evaluated safety and immunogenicity. The Japanese data were submitted after the application was filed, with a cutoff date of January 5, 2021. SAFE was then granted. At present, three drugs have been newly approved in Japan for COVID-19, two of which were granted approval under the SAFE system (**Table 1**).

In this paper, I review the Japanese SAFE system for COVID-19 drugs, including past cases, and discuss future issues.

What Is the SAFE System?

In Japan, the time from application to approval is generally about one year. In contrast, SAFE is granted in emergency situations such as pandemics. The approval system is based on Item 1, Article 14-3 of the Pharmaceuticals and Medical Device Act and allows for the approval of drugs earlier than usual. In other words, SAFE is a contingency drug approval system for emergencies arising in Japan. To be granted SAFE, the following requirements must be met:

1. The drug will help prevent the spread of a disease that is likely to seriously impact the lives and health of the Japanese public. The drug must be urgently needed to prevent the spread of the disease.
2. There is no drug available other than the drug in question.
3. The drug has been approved in a foreign country that has an approval system of equivalent rigor to that of Japan.

History of the SAFE System in Japan

SAFE has been applied to four drugs in Japan so far, including Pfizer's vaccine (**Table 2**).

First, in May 2010, GlaxoSmithKline (GSK) and Novartis vaccines received SAFE for the first time to treat a new strain of

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influenza (subtype A hemagglutinin type 1 and neuraminidase type 1 (H1N1)).[4,5] Subsequently, Gilead's remdesivir was granted SAFE in May 2020 to treat COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.[6,7] In February 2021, the tozinameran vaccine against COVID-19 was approved. So far, a total of four drugs have been granted SAFE in Japan.

The MHLW has decided that documents that would normally be required at the time of a new drug application for approval but that were not submitted in time for the SAFE can be submitted after the approval is granted. The two vaccines against subtype A H1N1 were approved and discontinued in March 2011, as the H1N1 influenza pandemic was less severe than expected and has subsided. The two vaccines against H1N1 subtype A influenza were removed from the registration of drugs master file in March 2011 and submission of reports for re-examination was discontinued.

Approved Drugs for COVID-19 and Approval Systems Other than the SAFE System in Japan

On April 23, 2021, a third drug against COVID-19 was approved by the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan, and **Table 1** lists the pharmaceutical drugs approved in Japan to date. As mentioned above, remdesivir and COVID-19 vaccine were approved by the SAFE system, while the recently approved baricitinib was approved under the regular approval system with a Priority Review and approved in 119 days. This approval was based on the following guidance:

> Handling of the approval review of pharmaceuticals, medical devices, *in vitro* diagnostic products, and regenerative medicine products during the pandemic of COVID-19 (April 13, 2020).
>
> Treatment of pharmaceuticals for COVID-19 during the approval review process (May 12, 2020)

The PMDA is conducting an urgent and flexible approval review process for drugs used against COVID-19.[8] Further, *in vitro* diagnostics, antigen tests, etc. related to COVID-19 are in the field of medical devices and are similarly being reviewed in a very prompt and timely manner.[9] Of course, the review of pharmaceutical drugs is also conducted promptly, but the difference between SAFE approval and the priority review of a regular approval such as that of baricitinib is unclear. The difference is that the review period is shorter for SAFE, and the reasons for differences between approval systems should be examined in detail.

Postmarketing Commitments and Risk Management Plan for Drugs Approved Under the SAFE System in Japan

The significance of the SAFE system for delivering necessary drugs in emergency situations is widely recognized. On the other hand, some issues need to be addressed.

SAFE is granted on the condition that the drug has been approved in other countries that have approval systems equivalent to that in Japan. Drugs that have only been used domestically, such as in clinical research, will not be eligible unless they have already been approved overseas. In fact, in 2020, a compound that originated in Japan, favipiravir (indicated for the treatment of influenza), was not subject to SAFE and has yet to be approved, although the government stockpiled the drug at a cost of ¥14 billion before approval.[10] Besides, if Japan were to pioneer the development of a drug for the treatment of COVID-19, that drug would not be eligible for approval under the SAFE system. In other words, SAFE requires prior approval overseas, so there is no mechanism for allowing an independent risk-benefit assessment exempting that requirement. The postapproval review process is also an issue. Since the decision on whether to grant SAFE is based on limited data, regulatory authorities should carefully monitor postmarketing data. **Table 3** summarizes the postapproval conditions and risk management plans for the two drugs approved for COVID-19.

The H1N1 influenza vaccines were canceled from the master file of registered drugs one year after approval, and postmarketing surveillance data were not disclosed. In Japan, a Risk Management Plan (RMP) has been required to be prepared and disclosed since 2013 in accordance with the "Guidelines for Drug Risk Management Plans;"[11] prior to that time, disclosure of an RMP was not mandatory. In addition, interim data from the postmarketing surveillance of H1N1 influenza vaccines, which were approved in 2010, have not yet been disclosed because the approval process was under re-examination, although it is a good time to disclose the re-review reports.

Some sort of system for providing approvals in cases of emergency is of course important. However, after approval, it is necessary to ensure that postmarketing activities are conducted in accordance with the RMP and the conditions of approval, to disclose the results in a timely and speedy manner, and to judge the appropriateness of continued approval based on the results of postmarketing activities.

Comparison of Emergency Use Systems in other Countries With the SAFE System in Japan

Each country has its own system for early approval under emergency conditions. The United States has the Emergency Use Authorization (EUA) system, requiring a declaration by the Secretary of Health & Human Services. The EUA permits the use of unapproved drugs or expands the existing indications for already-approved drugs when the following requirements are met:

1. The disease is life-threatening or causes serious illness
2. Efficacy of the drug for the disease is expected or recognized
3. The potential benefit to patients justifies the potential risks of treatment use and those potential risks are not unreasonable in the context of the disease or condition in question
4. There is no comparable or satisfactory alternative to diagnose, monitor, or treat the disease or condition in question

These requirements are similar to the SAFE system in Japan, but the risk-benefit analysis stated in the EUA is not described in the SAFE system, despite being a natural concept in approving a drug. Also, the EAU system differs from the SAFE system in that

Table 1 List of regulatory approvals and for drugs with indication for COVID-19 in Japan

No.	Brand name	Generic name	Indication	NDA date	Approval date	Review period (days)	Approval countries at NDA in Japan	Approval system in Japan	Period of re-examination	Company
1	Veklury	Remdesivir	Disease caused by SARS-CoV-2 infection (COVID-19)	May 4, 2020	May 7, 2020	3	United States (EUA)	SAFE	8 years	Gilead Sciences
2	Comirnaty	Tozinameran (mRNA vaccine)	Vaccine against COVID-19	Dec. 18, 2020	Feb. 14, 2021	58	United States (EUA)	SAFE	8 years	Pfizer
3	Olumiant	Baricitinib	Pneumonia caused by SARS-CoV-2 infection (patients requiring oxygen inhalation)	Dec. 25, 2020	Apr. 23, 2021	119	United States (EUA)	Priority review	Over 4 years	Eli Lilly

As of May 10, 2021.
COVID-19, coronavirus disease 2019; EUA, Emergency Use for Authorizations; mRNA, messenger RNA; NDA, New Drug Application; pts, patients; SAFE, Special Approval for Emergency; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

prior approval in another country is unnecessary. Further, the EUA can be approved using a lower standard of evidence ("reasonable to believe" that the drug "may be effective") than would apply to a regular approval.

The US Food and Drug Administration (FDA) in the United States has approved most drugs related to COVID-19 via the EUA.[12] For example, the antimalarial agents chloroquine and hydroxychloroquine were approved for COVID-19 by the EUA on March 28, 2020, remdesivir on May 1, 2020, and vaccines against COVID-19 by Pfizer and Moderna in December 2020.[13] Pfizer's vaccine is the first messenger RNA vaccine and was reviewed at an extremely fast pace, even though it carries a certain risk. Notably, the EUA approval for chloroquine was canceled after only 3 months.[13] This was because, after postmarketing data had been collected, the FDA concluded that the efficacy no longer outweighed the risks. The number of drugs approved by the EUA against COVID-19 alone is eight,[12] and the four Japanese SAFE cases enacted in 2010 are considered to be few. Japan has not utilized SAFE much during the pandemic.

The United Kingdom was also the first country in the world to apply an emergency use system for the vaccine against COVID-19, and the UK Medicines and Healthcare Products Regulatory Agency (MHRA) granted permission for the emergency use of Pfizer's vaccine on December 2, 2020.[14] Furthermore, the World Health Organization (WHO) gives emergency use listing.[15] If the vaccine is added to the WHO emergency use listing for developing countries that do not have a review system, developing countries will be able to use listed drugs as guidance when approving emergency use in their countries.

All of the above systems provide permissions for emergency use, not approval of the drug. In Japan, the SAFE is an approval system for marketing authorization of drugs. The European Medicines Agency (EMA) also has an approval system for emergency use in terms of marketing authorization. On January 6, 2021, the EMA conditionally approved the marketing authorization of the vaccine by BioNTech and Pfizer.[16] The EMA also considered emergency use[17,18] but had already started a rolling review of data from the clinical trials of vaccines against COVID-19, resulting in conditional approval.

Issues With the SAFE System in Japan

I believe that the main future challenge will be to consider emergency responses in normal times, rather than stopgap measures after an emergency such as when a pandemic occurs. To deliver medicines to patients as quickly as possible, there may be some medicines to which rules such as the SAFE system should be applied even in normal times.

SAFE is a system for approving drugs that have already been approved overseas, not for approving drugs originally developed in Japan. In the future, consideration may need to be given to the approval of drugs that have been developed only in Japan during a pandemic. Removal of the condition "The drug has been approved in a foreign country that has an approval system of equivalent rigor to that of Japan" from the SAFE criteria may be the optimal option. In this case, "the approved drugs in foreign countries," which is a kind of scientific criterion, is missing. Approval for emergency use is also

Table 2 Drugs approved by special approval for emergency in Japan

No.	Brand name	Generic name	Indication	NDA date	Approval date	Data package for NDA (completed studies)	Japanese patients in NDA package	Approval countries at NDA in Japan	US EUA	Period of re-examination	Company	Remarks
1	Arepanrix	Influenza A (H1N1) vaccine	Vaccine against Pandemic H1N1/09 virus	Oct. 16, 2009	Jan. 20, 2010	(1) Phase I/II Q-Pan-001 (United States, etc.) 680 pts (2) Phase III Q-Pan-002 (United States, etc.) 4,561 pts (3) Phase III D-Pan H1N1-007 (Belgium, etc.) 130 pts (4) Phase II D-Pan-H1N1-021 (Germany) 130 pts (5) Phase III H5N1-002 (Taiwan, etc.) 1,206 pts (6) Phase I H5N1-007 (Belgium) 400 pts (7) Phase III H5N1-008 (Germany, etc.) 5,075 pts (8) Phase II H5N1-009 (Spain) 138 pts (9) Phase II H5N1-010 (Belgium, etc.) 437 pts (10) Phase III H5N1-011 (Germany, etc.) 4,874 pts (11) Phase II H5N1-012 (Germany) 512 pts (12) Phase II H5N1-015 (Belgium) 350 pts (13) Phase II H5N1-022 (Spain) 266 pts	(Done) Phase II Q-Pan-011 100 pts (Ongoing) Phase II Q-PanH1N1-016 100 pts Phase II Q-Pan-H1N1-029 60 pts	EMA, Canada	No	8 years	GSK	Mar. 2011: Cancellation of drug registered in master file
2	Influenza HA vaccine H1N1 Novartis	Influenza A (H1N1) vaccine	Vaccine against Pandemic H1N1/09 virus	Nov. 6, 2009	Jan. 20, 2010	(1) Phase I V110_02 (United Kingdom) 176 pts (2) Phase I/II V89P01 (Germany) 753 pts (3) Phase III V110_03 (Germany, etc.) 812 pts (4) Phase III V110_04 (Belgium, etc.) Ongoing	(Ongoing) V110_05 200 pts V110_08 120 pts	Germany Switzerland	No	8 years	Novartis	Mar., 2011: Cancellation of drug registered in master file
3	Veklury	Remdesivir	Disease caused by SARS-CoV-2 infection (COVID-19)	May 4,2020	May 7,2020	(1) Phase III NCT04280705 (United States, etc.) 400 pts (2) Phase III GS-US-540-5773 (United States, etc.) 2,400 pts (3) Compassionate use (United States, etc.) 163 pts Others ・ Healthy volunteer safety studies ・ Phase II/III study for Ebola disease	(Done) Compassionate use 9 pts	United States	Yes	8 years	Gilead Sciences	Jan. 2021: Revision of package insert. Expand indication (Severe + Moderate disease).
4	Comirnaty	Tozinameran (mRNA vaccine)	Vaccine against COVID-19	Dec. 18, 2020	Feb. 2021	(1) Phase I/II/III C4591001 (United States, etc.). Phase I part 195 pts, phase II/III part 43,651 pts	(Ongoing and rolling submission of interim data). Phase I/II C4591005 160 pts	Umoted States	Yes	8 years	Pfizer	Age range is planned to be expanded (from 12 years old) by revising package insert

COVID-19, coronavirus disease 2019; EMA, European Medicines Agency; EUA, Emergency Use for Emergency; H1N1, hemagglutinin type 1 and neuraminidase type 1; mRNA, messenger RNA; NDA, New Drug Application; pts, patients; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 3 Postmarketing conditions of drugs granted special approval for emergency for the management of COVID-19 in Japan

Brand name	Generic name	Indication	Approval condition	Pharmacovigilance measures	Risk minimization plan	Safety specification			Company
						Important identified risks	Important potential risks	Important missing information	
Veklury	Remdesivir	Disease caused by SARS-CoV-2 infection (COVID-19)	(1) The applicant should develop and implement a Risk Management Plan. (2) The drug is granted Special Approval for an emergency situation, in accordance with the Pharmaceuticals and Medical Devices Act. There is extremely limited clinical experience with the drug. Therefore, after entry to the market, the applicant is required to promptly collect efficacy and safety data for the drug (e.g., adverse drug reaction information) from all patients treated with the drug, wherever possible, until data are gathered from a certain number of patients, and to take necessary actions to ensure the proper use of the drug. The applicant is also required to periodically report the information obtained. (3) The applicant is required to take actions necessary for the proper use of the drug, based on the results of an additional safety assessment of the drug. (4) The applicant is required to take actions so that updated efficacy and safety information on the drug is easily accessible to healthcare professionals. (5) The applicant is required to request that physicians administer the drug only to patients considered eligible for treatment with the drug who, or whose legally acceptable representatives, have been provided with the efficacy and safety information of the drug in written form, and who have provided written informed consent before the treatment. (6) Under Article 41 of the Ministerial Ordinance for Enforcement of the Pharmaceuticals and Medical Devices Act (Ministry of Health and Welfare (MHW) Ordinance No. 1 of 1961), the grace period for data submission is 9 months after approval. The applicant is required to submit the results of currently ongoing clinical studies at the earliest convenience when they become available. The applicant is also required to submit other data to the Pharmaceuticals and Medical Devices Agency (PMDA) at the latest within 9 months after the approval. If newly submitted data, etc., necessitate any changes in the approved drug information, a change in the approved drug information may be ordered in accordance with the provision in Article 74-2, Paragraph 3 of the Pharmaceuticals and Medical Devices Act.	(Routine pharmacovigilance activities) • Implementation of safety measures based on the collection, evaluation, and analysis of adverse drug reactions, information from literature and academic societies, and reports of foreign countries (additional pharmacovigilance activities) • Early postmarketing phase vigilance • Postmarketing surveillance (GS-JP-540-9009) • Multi-regional clinical phase III study of patients with moderate COVID-19 (GS-US-540-5774) • Multi-regional clinical phase III study of patient with severe COVID-19 (GS-US-540-5773) • No plan for efficacy	(Routine risk minimization activities) • Package insert (additional risk minimization activities) • Provision of information on early postmarketing phase vigilance • Preparation and distribution of medical materials for healthcare professionals (including informed consent) • Preparation and distribution of materials for patients • Periodic disclosure of adverse drug reactions	Acute kidney injury Liver disfunction Hypersensitivity (including infusion reaction, anaphylaxis)	None	Safety for approved dosage administration	Gilead Sciences

(Continued)

Table 3 (Continued)

Brand name	Generic name	Indication	Approval condition	Pharmacovigilance measures	Risk minimization plan	Safety specification: Important identified risks	Safety specification: Important potential risks	Safety specification: Important missing information	Company
Comirnaty	Tozinameran (mRNA vaccine)	Vaccine against COVID-19	(1) The applicant should develop and implement a Risk Management Plan. (2) The drug is granted Special Approval for Emergency, in accordance with the Pharmaceuticals and Medical Devices Act. There are extremely limited data for long-term stability with the drug. Therefore, after entry to the market, the applicant is required to continuously collect the stability data and to report the information obtained. (3) Clinical experience with the drug is extremely limited. Therefore, after entry to the market, the applicant is required to promptly collect safety data for the drug (e.g., adverse drug reaction information) should be collected at an early stage based on a predetermined plan, and submitted to the PMDA to take necessary measures for proper use of the drug. In so doing, information obtained from health surveys, etc., conducted by the government should also be reflected appropriately. (4) When the results of clinical trials currently being conducted or planned in Japan and overseas are obtained, the results shall be promptly submitted to the PMDA, and necessary measures shall be taken to make the latest information on the efficacy and safety of clozapine readily available to healthcare professionals and vaccinated persons. In addition, appropriate cooperation should be provided to the government in disseminating information on the efficacy and safety of this drug. (5) At the time of inoculation with clozapine, taking into account the fact that information on the efficacy and safety of clozapine will continue to accumulate in the future, physicians should provide appropriate explanations so that the latest information on efficacy and safety is explained in writing to the inoculated person or the substitute in advance, and written consent is obtained through a preliminary examination form, etc. (6) The grace period for submission of data based on Article 41 of the Pharmaceutical Medical Devices Law Enforcement Regulations shall be 6 months from the date of approval. In the event that it is deemed necessary to change the approved items based on the materials submitted in accordance with 2, 3, or 4 above, the approval period shall be 6 months from the date of approval. In the event that it is deemed necessary to change the approved items based on the materials submitted in accordance with 2, 3, or 4 above, an order to change the approved items may be issued in accordance with Article 74-2, Paragraph 3 of the Pharmaceutical Affairs and Medical Devices Law.	(Routine pharmacovigilance activities) • Implementation of safety measures based on the collection, evaluation, and analysis of adverse drug reactions, information from literature and academic societies, and reports of foreign countries (additional pharmacovigilance activities) • Early postmarketing phase vigilance • Postmarketing clinical study (C4591005) • General use results survey (follow-up survey) for vaccinated persons (healthcare professionals) who are vaccinated in the early postmarketing phase (C4591006) • Specific results of use study in subjects with underlying diseases considered to be at high risk for severe COVID-19 (C4591019) • Overseas clinical trial (C4591001) • Overseas clinical phase II/III study in pregnant women (C4591015) • No plan for efficacy	(Routine risk minimization activities) • Package insert • Guide for vaccine recipients (additional risk minimization activities) • Provision of information on early postmarketing phase vigilance • Preparation and provision of materials for healthcare professionals (Appropriate Use Guideline) • Preparation and provision of materials for vaccinated persons (for those who will receive the tozinameran COVID-19 vaccine, and their families) • Periodic disclosure of adverse drug reactions	Anaphylaxis	Vaccine-associated enhanced disease (VAED) Vaccine-associated enhanced respiratory disease (VAERD)	Safety for pregnant women or maternal women	Pfizer

COVID-19, coronavirus disease 2019; mRNA, messenger RNA; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

expected to be based on incomplete and interim clinical trial results (e.g., clinical trials with biomarkers, surrogate end points, and/or limited safety data). Similar to the case of conditional approval systems in Japan,[19] approval may have to be conditional on the adequacy and limitations of surrogate end points and postmarketing supplementation of safety data. However, Japan has been a member of the International Council on Harmonization since its establishment, and the regulatory agency of Japan is capable of approving drugs.[20]

Also, Japan has two existing, well-structured postmarketing systems for drugs. One involves pharmacovigilance and risk minimization activities according to the RMP. The other involves implementation of conditions of approval, where postmarketing commitment is a condition of approval. Ensuring that these postmarketing systems are implemented for drugs approved by the SAFE system seems warranted. However, the results of the postmarketing activities and the results of conditions of approval are usually disclosed when the re-examination application is approved. This means the results will be disclosed 8–10 years after approval. Since drugs approved under the SAFE system are likely to become the focus of public attention, enhanced transparency and speedy and timely disclosure of results can be considered necessary. In addition, it is necessary to disclose the results at an early stage, such as in periodic safety reports, rather than after the end of the re-examination period as is usually the case with ordinary drugs. Hence, it is important to judge the appropriateness of continued approval based on the results of postmarketing activities.

Conclusions

This review has summarized the SAFE system and approval situations of drugs for COVID-19 in Japan. As a result, the following issues and suggestions were identified:

1. SAFE is a system for approving drugs that have already been approved overseas, not for approving drugs that have been originally developed in Japan. A system to approve drugs that have not been approved in foreign countries needs to be established from a risk-benefit perspective for application in emergency situations. It would be better to remove the condition "The drug has been approved in a foreign country that has an approval system of equivalent rigor to that of Japan" from the SAFE criteria.
2. It is necessary to ensure that postmarketing activities are conducted in accordance with the RMP and conditions of approval, to disclose the results in a timely and speedy manner, and to judge the appropriateness of continued approval based on the results of postmarketing activities.

"Prompt approval" is, of course, important from the perspective of patient access, but "prompt postmarketing data disclosure and implementation of confirmatory clinical trials" appear to be even more important for SAFE. Prompt disclosure of results from scientific verification is clearly very important.

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