

Part II The Japanese government's response to COVID-19

Chapter 8 Medicines and vaccines

COVID-19 was an infectious disease never before experienced by humankind, and its outbreak called for the development of new drugs that were effective against its pathogen, the novel coronavirus. The purpose of developing new medicines and vaccines is to improve the life and prognosis of individual patients and stop patients' conditions from worsening or to prevent the onset of disease symptoms. Supplies of medicines and vaccines can not only make people feel safe, but also help prevent a collapse of the medical care system.

This chapter examines the basic system for development and production of medicines and vaccines, as well as the Japanese government's initial response and its moves related to approving medicines such as Remdesivir and Avigan and securing vaccines for the novel coronavirus disease.

1. Outline of the system for developing medicines and vaccines

1.1. The system for development, approval, production and supply

It is said that research and development for a medicinal drug takes more than 10 years.¹ A pharmaceutical company also needs to get approval from the health minister to manufacture and sell a new drug. The Pharmaceutical Affairs Law defines tests carried out to procure data necessary for obtaining approval for the manufacturing and sale of drugs as a clinical trial. Such a study must be carried out scientifically and with top priority placed on protection of the participants' human rights. It must observe Good Clinical Practice (GCP).^{2,3} Figure 1 shows the process of research and development and approval for a new drug.

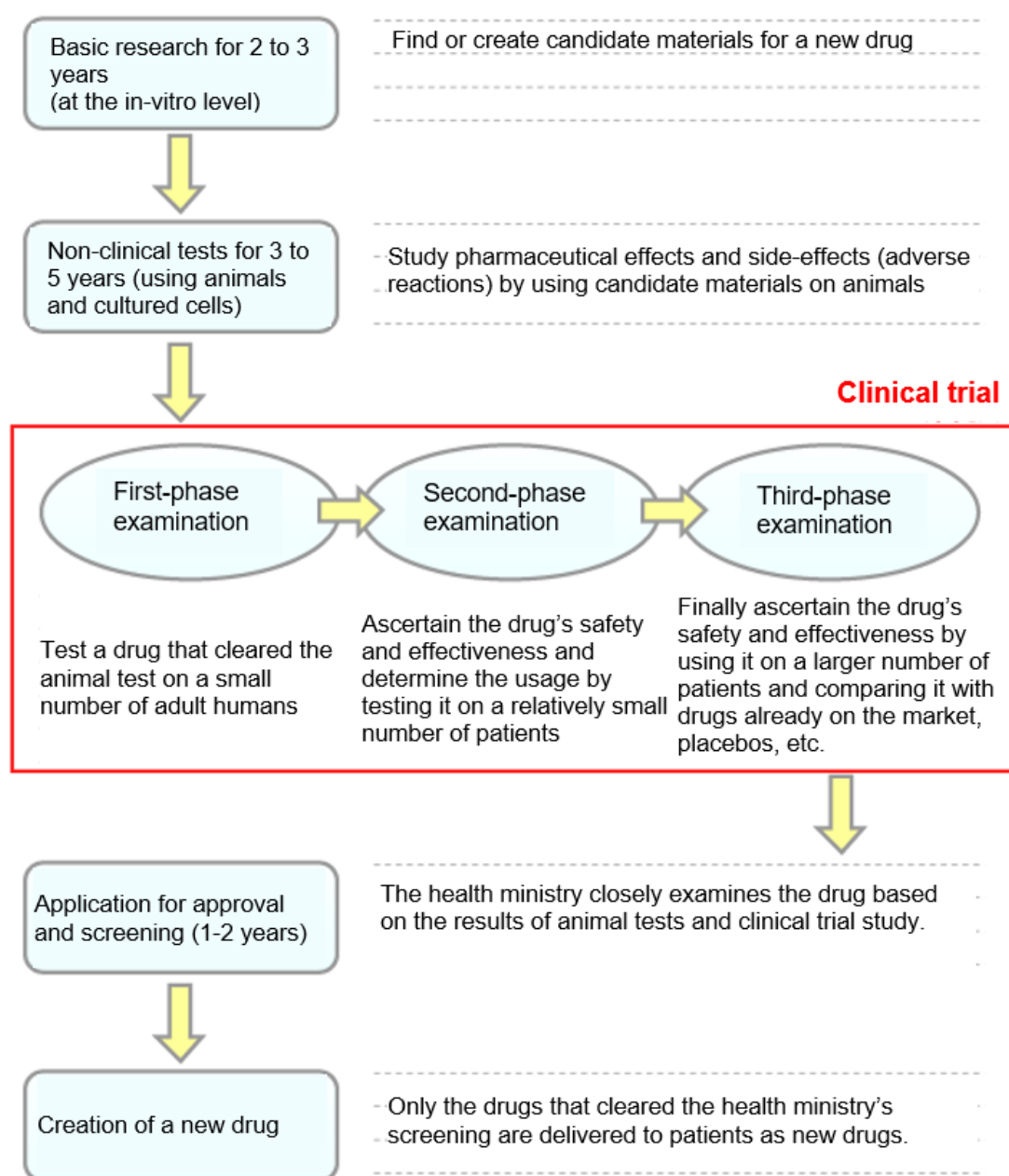
Although the domestic pharmaceutical industry manufacturing and supplying medicines constitutes one of the few global centers of drug development, each of the companies in the sector is relatively small in scale, while the cost of drug development continues to soar. Many large pharmaceutical firms rely on drugs whose patent has expired⁵ for their profits, and it is urgently needed for them to change their business strategy.

Some of the basic drugs have become unprofitable due to the repeated cuts in pharmaceutical prices under Japan's public health insurance system, forcing some manufacturers to stop production and raising doubts as to their stable supply – a problem that needs to be addressed. The generic drugs market has many small-scale manufacturers, and steps need to be taken to bolster their management. In view of such a situation and

problems in this sector, the Health, Labor and Welfare Ministry has been taking steps to increase productivity in the pharmaceutical industry and improve its manufacturing infrastructure, such as setting down new methods for managing the quality and safety of medicines in line with innovation in production technology and promoting the speedy introduction of the latest technology.⁶

Efforts to develop medicines and vaccines for the novel coronavirus started in January 2020 under this system of development, approval, manufacturing and supply of new drugs.

Figure 1: Process of R&D of a new drug and its approval⁴



1.2. Response in the initial stage

1.2.1. Start of developing medicines and vaccines

The outbreak of the novel coronavirus disease in China triggered various international attempts at developing medicines and vaccines for the new disease. The Coalition for Epidemic Preparedness Innovations (CEPI),⁷ in whose creation Japan's health ministry was involved and for which it has been providing funds since 2017, concluded a partnership agreement⁹ with three entities⁸ on January 23 to promote the development of vaccines against COVID-19 and promptly lead a candidate vaccine into a clinical test.

Beginning February 13, Japan embarked on the development of antiviral drugs, recombinant protein vaccines and other materials, selecting potential medicines for the disease from among existing drugs based on structure analysis technology by distributing research funds through the Japan Agency for Medical Research and Development mainly to the National Institute of Infectious Diseases and the University of Tokyo's Institute of Medical Science as well as to partnerships with private-sector companies.

Around the same time, the government started collecting knowledge and information on the novel coronavirus with the support of Health and Labor Grants-in-Aid for Scientific Research and the grants-in-aid for scientific research (funds for promotion of special research projects) of the Japan Society for the Promotion of Science. It also launched efforts in collaboration with private-sector firms to establish technologies for development of the method for prevention, diagnosis and treatment of the disease, prioritized screening of gene-recombination tests related to the novel coronavirus, and provided funds to CEPI to support international cooperation for the speedy development of vaccines.

In the basic policy unveiled by its COVID-19 headquarters on February 25, the government pointed to the possibility that medicines for other viruses might be effective in treating the novel coronavirus, and said it would work on developing treatment methods, medicines, vaccines and a test kit for speedy diagnosis. Thus the development of medicines and vaccines became one of the government's top-priority policy challenges.

1.2.2. Search for and development of candidate drugs

On February 26, the Japanese Association for Infectious Diseases issued the first edition of "How to consider the use of antiviral drugs in the treatment of COVID-19?" and presented drugs including Avigan (Favipiravir) as candidate medicines based on their availability in Japan, adverse reactions and other factors. It also said there was a good

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chance that new information could be obtained regarding choices of antiviral drugs for use in treatment of COVID-19 as well as their dosage and administration as knowledge and information on their clinical effectiveness and adverse reactions accumulated.¹⁰ In response to the growing demand for clinical studies to develop COVID-19 medicines and vaccines, Education, Culture, Sports, Science and Technology Minister Koichi Hagiuda announced on March 18 that the government would adopt a prioritized procedure, while taking steps to ensure safety, to substantially shorten the period for screening of research and development related to the novel coronavirus.

As these research and developments efforts proceeded, the search for candidate medicines moved forward, based on the knowledge and information accumulated through the treatment of COVID-19 patients from January. On March 23, the research group at the National Center for Global Health and Medicine engaged in “development of clinical treatment methods for serious cases” reported a plan to the government’s COVID-19 headquarters to start administering candidate medicines to patients of the disease at some medical institutions. According to the group, Avigan (or Favipiravir, already approved in Japan to be set aside for stockpiling for the treatment of influenza), Karetora (or Lopinavir or Ritonavir, already approved in Japan for HIV treatment) and Remdesivir (not yet approved either in Japan or abroad, and for treatment of Ebola hemorrhagic fever or EHF) would be administered to patients deemed to require them for an observational study.¹¹ It said the number of medical institutions taking part in the observational study would be expanded in stages with sufficient attention being paid to safety.

On March 28, the government headquarters adopted a basic policy to deal with the novel coronavirus, which said that “at present, no specific antiviral medicines or vaccines confirmed to be effective” against the disease existed and that “symptomatic therapy constitutes the central part of the treatment” of COVID-19 patients. It also said, however, that some of the existing drugs had been selected as candidate medicines and that “observational study using them on patients and other efforts are underway.” According to the policy, the health ministry, in cooperation with other government bodies and related institutions, was to “accelerate development of effective medicines and vaccines and promptly carry out clinical studies and trials regarding existing medicines for other diseases that are hoped to be effective” against the novel coronavirus.

The policy thus endorsed the approach presented by the National Center for Global Health and Medicine of developing drugs for COVID-19 through the use of existing drugs such as Avigan in clinical tests and through other efforts in the search for candidate medicines. In a meeting of the government headquarters on the same day, Prime Minister Shinzo Abe said that preventing the spread of infections, building a system to provide medical care for patients and developing medicines for the disease would be the key pillars of the government’s response to COVID-19, pledging to accelerate the research and development of medicines and vaccines as a top priority.

Experts in infectious diseases supported this stance of the government. The “analysis and recommendations” released by the government’s Expert Meeting on the

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Novel Coronavirus Disease Control on April 22 said the government bodies involved and related institutions needed to work together to keep up the efforts for developing effective medicines and vaccines. “Since a certain period of time is needed before approval is given to the manufacturing and sale of drugs, it is necessary to consider quickly using candidate drugs in medical practice while carefully examining adverse reactions and other matters, when candidate antiviral drugs are newly discovered and reported,” the expert panel said, adding that selection of appropriate medications for patients with a high risk of falling into serious conditions, as well as administration of such drugs before their conditions become serious, “should be carried out as research study.” Thus, the panel made it clear that development and discovery of medicines for COVID-19 should proceed through the appropriate use of the drugs as clinical research based on the consent of patients.

Figure 2: Establishing treatment methods/medicines and promoting development of vaccines¹²

· First, effective treatment methods and medicines will be developed to turn COVID-19 into a disease that people do not need to fear excessively. Then the development of vaccines, etc. will be pushed forward and research system developed in order to overcome the infectious disease.

	Issues	Countermeasures	Future direction
Clarifying mechanism of aggravation	<p><u>The mechanism of the disease's aggravation has not been clarified.</u></p> <p>While most patients do not develop symptoms or are mild cases, the mechanism of the disease's aggravation was not known.</p> <p>No aggravation markers existed that could be used to prevent the patients' conditions from becoming serious by intervening at an early stage.</p>	<p>The guideline for treatment revised on May 18 pointed out that signs showing progress of the disease from asymptomatic condition to medium-level symptoms contain items that may serve as markers of aggravation.</p> <p>Research needs to be carried out to establish aggravation markers that are more accurate.</p>	<p>In addition to expanding the testing system, patients will be detected without fail at an early stage of the disease through early diagnosis, and aggravation of patients' conditions and their death will be prevented through early intervention.</p> <p>Efforts will be made to turn COVID-19 into a disease about which people do not need to have an excessive fear.</p>
Developing treatment methods and medicines	<p><u>Absence of treatment methods and medicines</u></p> <p>No established medicines for the new infectious disease existed.</p> <p>Clinical conditions like thrombosis to which attention must be paid in treatment are gradually becoming clear.</p>	<p>Remdesivir has already been approved under the law on drugs and medical instruments. Appropriate measures have been taken to secure its stock and supply so that the drug will reach patients who need it.</p> <p>Clinical trial and other efforts are underway for Favipiravir (Avigan), Ciclesonide and other drugs with a view to early approval.</p> <p>Examination of the</p>	<p>Clinical research will be carried out with a view to developing quick-result and efficient aggravation markers, treatment methods, medicines, etc.</p>

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		<p>effectiveness and safety of existing medicines, etc. and development of new drugs will be carried out, using the fiscal 2020 extra budget and other funds.</p> <p>Relevant knowledge and information will be collected and a guideline for treatment will be revised so that clinical conditions like thrombosis that deserve attention will be dealt with.</p>	
Development of vaccines	<p><u>Vaccines do not exist</u> Vaccines against COVID-19 do not exist because it is a new infectious disease. (No effective vaccines exist against MERS and SARS exit yet.)</p>	<p>With sufficient funding, vaccines with excellent effectiveness and safety will be developed. The production infrastructure will be built simultaneously. Preparations will be made to build a system so that necessary vaccines will be secured as quickly as possible and that inoculation will be promptly carried out.</p>	<p>Along with domestically developing COVID-19 vaccines as soon as possible, systems for supply and inoculation of the vaccines will be strengthened and developed.</p>
Research infrastructure	<p><u>Insufficient research system</u> The research infrastructure is weak since Japan has fewer specialists than other countries. Research to elucidate conditions by collecting clinical specimens and research that flexibly responds to changing circumstances are insufficient.</p> <p>Since doctors are extremely busy with medical care and other tasks and there are not enough research assistants, valuable clinical data become scattered and lost.</p> <p>Research institutes are unfamiliar with application of exceptive clauses of laws and guidelines concerning public health crises.</p> <p>At public health institutes, time spent on research and personnel are insufficient because they are busy with testing and communicating with other organizations.</p>	<p>A system to collect clinical information and other data needs to be established so that valuable information will not be scattered and lost. An adjustment function to instantly respond to a pandemic is needed.</p> <p>It is necessary to secure personnel and establish infrastructure, etc. by using direct expenses.</p> <p>Protection of people subject to study in research should be given top priority. A system needs to be built in which research institutes and ethics committees will properly apply exceptive clauses of laws and guidelines in order to speedily conduct high-quality research.</p>	<p>An all-Japan system for research on infectious diseases will be built to quickly and flexibly plan research projects, collect scattered data and coordinate various research activities. National Institute of Infectious Diseases and the National Center for Global Health and Medicine will take the lead in building such a system in cooperation with academic society and other related organizations by securing necessary human resources and funding.</p>

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Later, as efforts continued for developing medicines and vaccines and screening for their approval, the expert panel on May 29 reiterated the need for such efforts and pointed out that “although Japan pursued measures to tackle pandemics through such steps as the enactment of the Act on Special Measures for Pandemic Influenza and New Infectious Diseases Preparedness and Response and preparing a government action plan since the outbreak of new-type influenza in 2009,” the nation now has to respond to COVID-19 in the absence of effective medicine or vaccines or easily usable test kits. Recognizing that the lack of medicines and vaccines hampers the response to the novel coronavirus, the panel said that “effective treatment methods and medicines must first be developed so that people do not need to have an excessive fear of the disease” and that further efforts should be made to overcome COVID-19 through the development of vaccines and beefing up research on the disease.

1.3. Budgetary measures for developing medicines and vaccines

With regard to the development of medicines and vaccines for the novel coronavirus, the government set aside a total of ¥144.4 billion in five rounds from February 13 to May 27 to pay for research and development related to COVID-19.¹³

Table 1: Outline of the budget¹⁴

Timing	Amount	Outline
Feb. 13, 2020 (1 st round)	¥2.03 billion	Immediately start developing methods of diagnosis and treatment as well as vaccines based on knowledge/information on SARS, MERS and other infectious diseases by using leftover from fiscal 2019 budget and reserve funds
March 19 (2 nd round)	¥3.11 billion	Accelerate clinical research for utilization of existing drugs for treatment of COVID-19 and development of quick testing devices, and build an R&D platform that can quickly respond to the spread of a new infectious disease, by using the discretionary reserve fund and adjustment fund for research and development in the medical field for fiscal 2019
April 17 (3 rd round, the first adjustment expense in fiscal 2020 for R&D in the medical field)	¥3.25 billion	Further accelerate and expand research and development related to the novel coronavirus disease through top-down expense allocation in view of the pressing need for developing new drugs and vaccines as well as medical instruments
April 30 (4 th round, the first supplementary budget for fiscal 2020)	¥75.1 billion	Efforts added to further accelerate development of equipment and systems in addition to development of treatment methods and vaccines for COVID-19 in order to overcome the disease and put the economy back on a recovery track

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May 27 (5 th round, the second supplementary budget for fiscal 2020)	¥60.9 billion	Support for development of vaccines; Development of medicines by means of a new mechanism of action; Development of diagnosis and treatment methods based on new research; Research study projects aimed at response to resurgence of infections
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2. Approval of medicines

2.1. Remdesivir – Clinical trial study and approval in the U.S. and unusually speedy approval in Japan (May 7)

On February 26, Gilead Sciences started a clinical test¹⁵ to evaluate the safety and efficacy of Remdesivir for use in treatment of adults who were diagnosed with the novel coronavirus. In its April 10 announcement, the company said that the analysis of the result of administering Remdesivir to patients for humanitarian purposes showed clinical improvement in a majority of the patients and no signs of new concerns over their conditions. As a consequence, the company decided to carry out further examination through a number of clinical tests.¹⁶

On April 29, the National Institute of Allergy and Infectious Diseases (NIAID) of the United States announced that large-scale clinical tests of the antiviral drug Remdesivir, now closely watched as a medicine for the novel coronavirus, showed that compared with a placebo, the drug reduced the time of recovery of COVID-19 patients by more than 30 percent. NIAID Director Anthony Fauci said that the tests proved “clear-cut” effects of Remdesivir.¹⁷ The details of the tests were published in the *New England Journal of Medicine*, the world’s most authoritative medical journal.¹⁸

This led to Emergency Use Authorizations (EUA) on May 1 of the drug for its use in treating COVID-19 in the U.S.¹⁹ With the EUA, it became possible to widely use Remdesivir as a drug for COVID-19 inpatients with serious conditions.²⁰ On the other hand, the EUA noted that Remdesivir was a drug still in the process of development and had not yet received approval of the U.S. Food and Drug Administration.²¹

Following the issuance of the EUA for Remdesivir in the U.S., an application was submitted on May 4 for approval under the Pharmaceutical Affairs Law for use of the same drug in treating COVID-19 in Japan. The health ministry carried out the screening the same day and it was decided with unusual speed that the Pharmaceutical Affairs and Food Sanitation Council would be consulted. If the council grants an approval, use of a drug in Japan becomes possible, with points of attention, such as eligibility and exclusion criteria, shown concerning use of the drug in question. However, in view of strong demand for the drug worldwide, the health ministry assumed that its supply might

be limited. To prepare for a situation in which Japan could get only a limited supply of the medicine, and in order to grasp the amount of the drug domestic medical institutions would need in case its approval was granted, the ministry requested prefectural governments, major cities with public health centers under their jurisdiction and the public health divisions of Tokyo's special wards to send internet-based questionnaires to the hospitals concerned.²²

On May 7, the health ministry granted special approval²³ to Remdesivir based on Article 14-3 of the law on securing the quality, effectiveness and safety of medical drugs and instruments, after the second medical drugs division of the Pharmaceutical Affairs and Food Sanitation Council earlier in the day gave its nod to Gilead Sciences' application for approval of Remdesivir under the Pharmaceutical Affairs Law. In granting the approval, the ministry limited the use of the drug to patients with serious conditions.²⁴
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At the meeting of the council's Second Medical Drugs Division, Hiroshi Kiyota, division chief, gave a general overview by saying, "There are many problems because this is a special exception. Because information on the medicine's efficacy and safety is limited, we are waiting for the verification of its efficacy and safety now being conducted in a clinical trial. I believe that there will be an announcement as soon as it is known. Therefore, thorough measures must be taken to safely use the drug. On the other hand, I believe that you all recognize the importance of quickly securing chances to use the drug for treatment in Japan as well." Thus the division gave the go-ahead for approving the drug.²⁶ The approval came only three days after Gilead Sciences applied for approval on May 4. This was an extremely exceptional and prompt response, as shown by the fact that the bureaucratic paperwork for approval by the division was done ahead of schedule to enable the division to approve the drug on the very day the division's meeting was held.

2.2. Avigan – Prime Minister Abe's statement and apprehensions expressed by experts

2.2.1. Attention focusing on the anti-influenza virus drug Avigan and launch of a clinical trial

Avigan is a drug originally developed by Fujifilm Toyama Chemical Co. as an anti-influenza drug. In two development stages (two I/II Phase tests and three III Phase tests, in which the drug was compared with a placebo or Oseltamivir²⁷), the drug's efficacy was observed in some cases but not in others. Furthermore, it was determined that the drug "should not be used on pregnant women or women with the possibility of being pregnant (contraindication)" because animal tests confirmed that the drug causes death or deformity in early embryos. As a consequence, the drug came to be handled as a

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“special” drug,²⁸ the use of which on patients would be considered only when a new type of influenza or a re-emerging influenza to which other anti-influenza virus drugs proved ineffective or insufficiently effective should break out and the government gave the go-ahead for its use against the virus in question.

On February 26, the Japanese Association for Infectious Diseases, in the first edition of its “How to consider anti-viral drug-based treatment of COVID-19?” presented a number of drugs including Avigan as candidate medicines for the novel coronavirus by taking into account the availability in Japan and adverse reactions of the drugs as of that date.²⁹ Behind the association’s suggestion was the fact that China, which suffered a mass outbreak of COVID-19 ahead of other countries, used a generic version of Avigan in the treatment of the disease and proceeded with a clinical test of the drug.

In late February, the health ministry gathered its officials from divisions concerned with the development of medicines and instructed them to look into Avigan’s efficacy against the novel coronavirus. Officials who attended the meeting said that they were told that they “did not need to reach a conclusion that the drug would work but needed to quickly make it clear whether it was effective or not” because both the public and the Prime Minister’s Office had high hopes of Avigan’s efficacy. In obtaining approval for a medicine, data with scientific evidence must be presented. While the major premise for honoring scientific rules was upheld, the health ministry was under pressure to draw a conclusion on Avigan’s efficacy as quickly as possible – to respond to the strong interest of the public and the Prime Minister’s Office.³⁰ This move by the health ministry helped lead Fujifilm Toyama Chemical to carry out a domestic Phase III clinical test of Avigan intended for COVID-19 patients beginning on March 31.³¹

2.2.2. Growing expectations for Avigan

In April, the government hurriedly launched efforts to secure domestic supply of Avigan although its clinical trial had not yet been completed. In order to build an integrated system of domestic supply following the drug’s approval under the Pharmaceutical Affairs Law, the government thought it necessary to enable production of Avigan with domestically procured raw materials and on April 2, requested Denka Co.³³ to produce diethyl malonate (DEM),³² a raw material for Avigan.³⁴

On April 6, the Japanese Association for Infectious Diseases carried reports on its website on cases in hospitals in Tokyo whose conditions were found to have rapidly improved and cases who were found to have turned negative in PCR tests after they were given Avigan.³⁵

As such cases were reported, the Prime Minister’s Office started to show strong interest in Avigan as a potential medicine for the novel coronavirus. The following day, on April 7, Prime Minister Abe held a news conference to declare a state of emergency

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under the Act on Special Measures for Pandemic Influenza and New Infectious Diseases and said, “Even amid great uncertainties with no sight of the future at all, hope is undoubtedly being born. Development of vaccines and medicines is making progress with corporations and researchers in Japan and all over the world mustering their wisdom. Avigan, which was approved as medicine for novel influenza and whose adverse reactions have been made known, has been administered to more than 120 patients [of COVID-19] and I have been informed that it has produced effects for improving the patients’ conditions.” He went on to say that the government planned to expand the use of the drug “as much as possible to patients who want it under an arrangement of observational study” and to achieve that, it would triple the stockpile of Avigan to a volume sufficient for 2 million people, adding that “businesses across the country have expressed their readiness to cooperate in producing the raw materials needed for increased production of the drug.” The prime minister thus made clear his intention to significantly increase the output of Avigan even though it had yet to be approved under the Pharmaceutical Affairs Law as a drug for the novel coronavirus.

On April 15, Fujifilm Toyama Chemical said it had begun to boost production of Avigan in response to the government’s decision to increase its stockpile of the drug to secure a supply for 2 million people³⁶ as part of its emergency economic package. Fujifilm Holdings Corp., its parent company, said it would take the following steps to meet the government’s call for increasing the domestic stockpile of Avigan and the requests from other countries for supply of the drug: reinforcing the group firms’ facilities to make intermediates necessary for the production of medicines; expanding the output of Avigan and boosting its production capacity in stages through tie-ups with companies both in Japan and abroad including raw materials manufacturers and firms cooperating in each production process, as well as beefing up its facilities to produce raw materials for Avigan to enhance their output capacity.³⁷

During this period, Prime Minister Abe is said to have strongly pushed for the use of Avigan – even as exception to the rule.³⁸ The Prime Minister’s Office pressed the health ministry beginning in mid-April to quickly grant an approval of Avigan.³⁹ Since Avigan had already been approved under the Pharmaceutical Affairs Law as an anti-influenza drug and its safety confirmed – despite a certain degree of adverse reaction – the Prime Minister’s Office was of the opinion that the use of the drug for COVID-19 should be allowed as an exception based on doctors’ judgment even if its effectiveness against the novel coronavirus disease was not strictly confirmed through clinical trials. However, Japan did not have a system to permit exceptional use of a medicine whose efficacy had not been confirmed in a clinical trial. Later, on May 12, the health ministry came to accept application for approval of drugs for treating the novel coronavirus even if they had not gone through clinical trials – on condition that their efficacy and safety were confirmed in public research projects that met international scientific and ethical standards, and that the data from the research projects were submitted.

On May 4, Prime Minister Abe said the state of emergency, which was originally scheduled to end on May 6, would be extended through May 31. At the news conference

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announcing the decision, he said, “Approval was given in the U.S. to the use of Remdesivir, which has been tested in a joint clinical trial study in Japan and the U.S. And today, an application was made in Japan for special approval of the drug. The government will promptly start the procedure for approval. Avigan, which was developed in Japan, has already been administered to nearly 3,000 patients and its clinical tests are making steady progress. If the drug’s effectiveness is confirmed on the basis of the data [from the clinical tests], we would like to grant approval to the drug under the Pharmaceutical Affairs Law so that it can be used with a doctor’s written prescription.” He said the government would aim for gaining approval of Avigan for use against COVID-19 by the end of May. Prior to the news conference, a high-ranking health ministry official told the prime minister that a special clinical trial that included an observational study and a clinical study by the manufacturer produced several hopeful reports concerning Avigan. However, since those reports were not conclusive, the official advised the prime minister to add a qualifier to his statement saying “If the drug’s effectiveness was confirmed,” instead of making a definite statement that approval would be granted without fail. Abe followed this advice in making his statement.⁴⁰

2.2.3. Warnings from experts and disappointing clinical trial results

As the public’s and politicians’ expectations for Avigan grew rapidly, the Japan Medical Association’s panel of experts on COVID-19 expressed apprehensions over these moves. The panel pointed out that in testing a drug for treatment of an unknown disease like COVID-19 – some of whose patients fell into serious conditions while others with mild symptoms naturally recovered – large-scale clinical tests involving a considerable number of patients were necessary, and that it was difficult to obtain meaningful results only through observation studies. “With regard to a candidate drug that does not have enough evidence [of its efficacy], especially a drug that is already on the market, exceptional approval should not be granted hastily,” the panel said, recommending that approval be given on the basis of “sufficiently scientific evidence collected through clinical trials.” The experts thus sounded a warning from their scientific standpoint against the rise in partially emotional expectations for Avigan.

A report was then published on the provisional analysis of the results of unblind, randomized clinical tests of Favipiravir (Avigan) to examine its effect in reducing the virus on asymptomatic patients of SARS-COV2 infection (COVID-19) and those with mild symptoms, which were carried out at 47 medical institutions across the country with Fujita Health University serving as the representative institution and Yohei Doi, professor at the university’s Infectious Diseases Department, serving as the principal investigating doctor. The report concluded that although the virus tended to disappear and fever was alleviated among patients who were given Avigan in a normal manner – compared with others who were given the drug with a delay – thus raising the possibility of Avigan having

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a certain degree of effect against the novel coronavirus, a statistically significant difference was not detected between the two groups. It thus concluded that the drug's effectiveness was not scientifically proven.

Among patients given Avigan from the first day of the tests, the time needed for the virus to disappear tended to be shorter than among those administered the drug from the second day, but the difference was not statistically significant.⁴¹ Given that the number of patients who took part in the tests was relatively small, at 89, however, and that one of them withdrew consent for the test and 19 others were excluded on the grounds that the virus had disappeared before the drug was administered, the possibility still remained that clinical tests involving much larger numbers of patients might prove Avigan's effectiveness. On September 23, Fujifilm Toyama Chemical announced that in the Phase III clinical test of Avigan against the novel coronavirus (JapicCTI-205238: tests different from the afore-mentioned clinical trial led by Fujita Health University), the time needed to alleviate fever, improve oxygen saturation and lung image findings, and turn the virus negative in PCR tests was shortened with statistical significance among the group of patients administered Avigan when compared with the control group.

The results of the clinical trial of Avigan as contained in the report, made public more than three months after the study began, fell far short of the expectations of the Prime Minister's Office. In Japan, it takes a certain period of time before clinical trial commence because the drug manufacturer needs to consult with the Pharmaceuticals and Medical Devices Agency (PMDA), develop a necessary in-house system and obtain consent from hospitals that will take part in the study. A senior health ministry official said that it took time for the clinical trial on Avigan due to these factors and also to obtain the results of the study.⁴²

2.2.4. Avigan and international public health diplomacy

Countries around the world were showing interest in Avigan from the initial stages of the spread of COVID-19. On March 28, Prime Minister Abe said that Japan would respond to such interest in the medicine by expanding the clinical study on Avigan in cooperation with countries that wished to participate and start boosting its output. He thus made clear his intention of supplying Avigan to other countries to expedite its clinical trial.

On April 7, the day the state of emergency was declared, Foreign Minister Toshimitsu Motegi said Japan had been directly requested by foreign ministers of various countries in telephone talks to provide Avigan, and indicated that the government would internationally expand the clinical trial of Avigan in cooperation with countries that wished to join (with a total of \$1 million in emergency grant aid). It was disclosed that Japan would provide Avigan free of charge through the United Nations Office for Project

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Services (UNOPS) to countries that would take part in the clinical trial, with arrangements already made for the free supply of the medicine within a certain framework to 20 countries, some 30 more nations in talks for such an arrangement. In a special videoconference of the ASEAN Plus Three leaders on April 14, some of the leaders referred to Avigan and Prime Minister Abe explained that the clinical trial would be expanded through the free supply of Avigan.⁴³ The number of countries that had requested the provision of Avigan through diplomatic channels reached nearly 80 as of May 15.

In providing Avigan to other countries, coordination was required between the health ministry, the Ministry of Economy, Trade and Industry and the Foreign Ministry, and the task was assigned to the economic team of the National Security Secretariat.⁴⁴ The Foreign Ministry received the requests from other countries for the provision of Avigan, and the decision as to which countries should get the supply, in what volume and in what order was made through coordination among the ministries. The health ministry was mainly in charge of coordination with Fujifilm Holdings, while METI was responsible for procurement of raw materials for the drug.⁴⁵

Some difficult issues needed to be sorted out before supplying a drug to the other countries whose effectiveness against the novel coronavirus had not yet been confirmed. Among them were disclaimers by the government and Fujifilm Holdings in case side effects of the drug emerged, as well as the method of transport for delivering the medicine.⁴⁶ Clinical tests would lose their value if the method of administering the drug and other matters were not properly managed, and the emergence of side effects due to use of the drug in ways not anticipated by the Japanese side might affect the evaluation of the clinical trial currently underway. It was therefore argued that free distribution of Avigan abroad carried a certain risk to both Fujifilm Holdings and Fujifilm Toyama Chemical. However, since the overseas provision of Avigan was a key component of Japan's public health diplomacy based on political judgment, a decision was eventually made for the government, despite those risks, to buy Avigan tablets from the Fujifilm group to deliver to the other countries and take responsibility for problems that might occur.

The Foreign Ministry secured the necessary budgetary allocation, drew up a model memorandum regarding the government's disclaimer and other matters to be concluded with the countries that receive the supply of Avigan, and weighed the method of delivery to those countries. The government proceeded with this operation by taking the intention of the Fujifilm group (or its strategy toward future approval of the drug) into account. At that time, a Chinese-made generic version of Avigan was being administered to patients in Wuhan and a research paper showing a certain degree of efficacy was published. One of the reasons the Fujifilm group cooperated with the government's operation was that officials of some countries who read the paper had directly approached the group.⁴⁷

3. Developing and securing the vaccines

3.1. Recommendations by the 2010 review meeting on measures against new-type influenza (A/H1N1) and Japan's vaccine policy

When the new type of influenza (A/H1N1) broke out and spread across the globe in 2009, the World Health Organization declared a pandemic of the novel influenza (pandemic alert phase 6) nine weeks after the first report on the outbreak. The new-type influenza became rampant in Japan and some 20 million were estimated to have contracted the virus between April 2009 and the end of September 2010. About 18,000 people were hospitalized and 203 people died.⁴⁸

To cope with the pandemic, the government took a budgetary measure to help vaccine manufacturers/distributors make capital investments and import the vaccines based on the basic policy (announced on October 1, 2009)⁴⁹ on inoculation of the vaccine against the new type of influenza (A/H1N1) with a view to developing and securing vaccines.⁵⁰ The final report of the meeting that looked back on measures taken against the pandemic influenza highlighted the need to review and examine problems in the systems and matters that required advance preparations as well as various operational challenges.⁵¹

In light of the review meeting's proposals, a panel of experts on the new type influenza recommended the inclusion of the following measures in the government's new action plan: promoting the study and development of vaccine production/medication methods, developing production lines, importing a great enough volume of vaccines to cover all the people in Japan in the case of a pandemic.⁵²

As patients of the novel coronavirus disease emerged and infections spread across Japan from January 2020, securing vaccines against the disease was put high on the policy agenda. At this point, Japan's vaccination policy had been updated in accordance with the afore-mentioned proposals made by the review meeting on the new-type influenza (A/H1N1) as shown in Table 2.

A senior health ministry official said that government subsidies provided for beefing up the system for developing/producing vaccines against novel influenza proved useful in coping with the latest novel coronavirus pandemic. Since production facilities had been updated with the subsidies, the vaccine manufacturers were able to use that equipment with some modifications to produce vaccines against COVID-19.⁵⁴

Table 2: Vaccine policy (revised action plan for pandemic influenza)⁵³

1.Promotion of advance preparation	<ul style="list-style-type: none"> • Promote study and development of production method for new vaccines, the medication method, etc., aiming to produce enough vaccines to cover all the people in Japan within six months • The principle is to secure an enough amount of vaccine by procuring domestically produced vaccines, but until the system for domestic production of the vaccines is developed, there is a need to look into ways to secure the vaccines through imports. • Build a system for smooth distribution of vaccines • Build an inoculation system to carry out group vaccinations in case the virus is highly pathogenic and infective
2.Quick response to an outbreak	<ul style="list-style-type: none"> • Identify matters to be decided and set down rules for making the decisions in advance as much as possible so that measures related to vaccines will be adopted promptly when a new type of influenza breaks out • Take into consideration the characteristics of the virus (pathogenicity, infectivity, etc.) in deciding on the legal status of vaccination and who should be given the priority in receiving the vaccination
3.Stockpiling of pre-pandemic vaccines	<ul style="list-style-type: none"> • Make it clear that vaccines will be stockpiled in advance in the form of finished products so that vaccination can be promptly carried out in case of the outbreak of a new type of influenza

3.2 Development of vaccines against the novel coronavirus

3.2.1. Competition among drug manufacturers and biotechnology companies in developing vaccines

Worldwide efforts to develop vaccines for the novel coronavirus are being led by major pharmaceutical companies. On April 29, Pfizer Inc., a U.S.-based pharmaceutical giant, and BioNTech SE of Germany announced that they had started joint development of a vaccine and had already finished the first dosing of a candidate vaccine in their Phase I and II clinical trial study tests.⁵⁵ On May 28, it was announced that Oxford University and AstraZeneca PLC of Britain had concluded a one-year contract for supply for clinical tests and commercial purposes to increase the production of AZD1222, a candidate vaccine developed by the university. Under the contract, the university was to continue to provide several candidate vaccines for the pharmaceutical firm through the end of 2020.⁵⁶

On July 27, Moderna, a U.S. biotechnology firm, started an unblinded, randomized test to compare the mRNA-1273 vaccine with a placebo as a Phase III clinical trial test.⁵⁷ The clinical test involving 30,000 people 18 and older was scheduled to end October 27, 2022. This vaccine was confirmed to be safe and to increase antibody valency in the Phase I clinical trial.⁵⁸ A test that used monkeys proved that the vaccine could

prevent pneumonia from a novel coronavirus infection.⁵⁹

Sanofi S.A., a major pharmaceutical company in France, is cooperating with GlaxoSmithKline PLC of Britain,⁶⁰ and Sinovac Biotech Ltd. of China is teaming up with Butantan Institute of Brazil, a vaccine manufacturer, and they are respectively developing vaccines and carrying out clinical tests.⁶¹ Pharmaceutical companies all over the world are thus competing to develop COVID-19 vaccines. According to the WHO, 26 candidate vaccines were in the stages of clinical tests and 139 other candidate vaccines were being studied in non-clinical tests as of the end of July 2020.⁶²

3.2.2. Development of vaccines in Japan

Compared with such tight competition abroad, development of COVID-19 vaccines in Japan was making slow progress. Japan was about “three and a half laps behind” other countries in vaccine development, according to a government official.

Unlike medicines administered to patients, vaccines to prevent contracting an infectious disease are for a much wider use – injection for individual healthy members of the population – and ensuring its safety is especially important in the development of a vaccine. It also requires highly advanced technology to measure the effect of immunity acquisition via the vaccination. Since vaccines are intended for broad use on the general population, unlike drugs administered to patients of diseases, serious side effects of a vaccine could lead to damages lawsuits on an extremely large scale. On the other hand, the size of the market for vaccines is only a fraction of the entire market for medical drugs. It is difficult for pharmaceutical companies to keep up the development of vaccines unless they have stable proceeds from the sale of other medical products. In addition, since vaccine manufacturers have an aspect of being a public industry supporting the foundation of government policy to combat infectious diseases, private-sector companies that take on the task are required to have the management strength to maintain the public-interest business. As a result, big players in the pharmaceutical industry play a central role in developing and producing vaccines both in Japan and internationally. In fact, four major drug manufacturers occupy about 90 percent (as of fiscal 2017) of the world's vaccine market (GlaxoSmithKline PLC with a market share of 24 percent, Merck & Co. 23.6 percent, Sanofi S.A. 20.8 percent and Pfizer Inc. 21.7 percent).⁶⁴

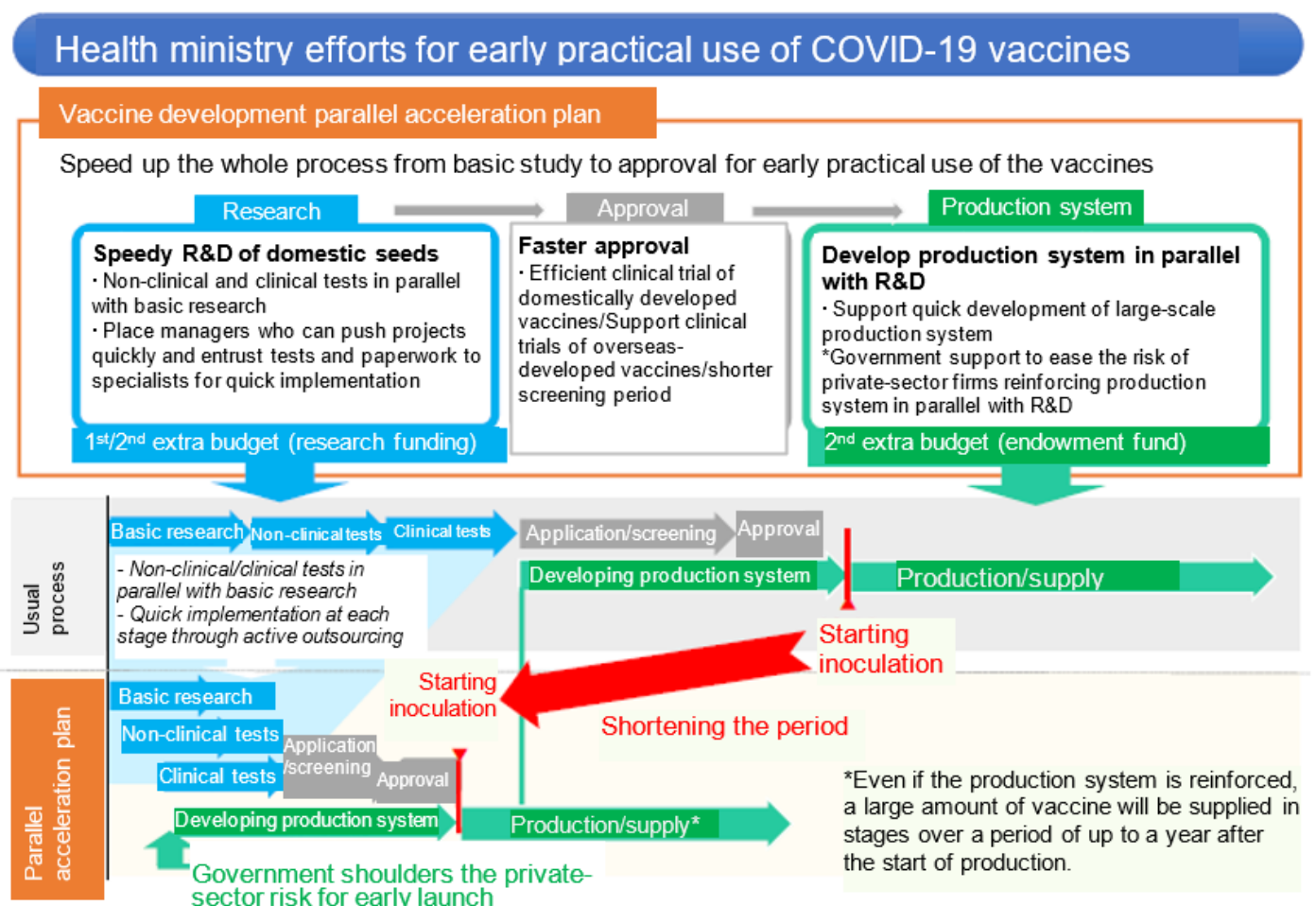
No Japanese pharmaceutical manufacturers enjoy such a large share in the global market. Even Takeda Pharmaceutical Co., Japan's largest drug manufacturer, holds 16th place in world ranking in terms of sales of pharmaceutical products in 2019.⁶⁵ Commenting on this situation, a government official said the health ministry had failed to make steady efforts to develop domestic vaccine manufacturers for the following reasons: since the vaccine industry was a high-risk sector, the health ministry did not take proactive steps to promote the industry, and the ministry, a regulatory government body,

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had few motivations to foster an industry under its jurisdiction.⁶⁶ Such an industrial structure may be to blame for Japan lagging behind other countries in the development of COVID-19 vaccines.

The government is taking steps to address the problem. Given the urgency of development and supply of vaccines for the novel coronavirus, the health ministry included appropriations in the second fiscal 2020 budget to accelerate vaccine research and development and to establish a system for quick production of vaccines and inoculations. The ministry calls this a “parallel acceleration plan” (See Figure 3) and aims to put the vaccines to practical use as soon as possible by speeding up the whole process from basic study and development of the vaccines to approval under the Pharmaceutical Affairs Law.⁶⁷

Figure 3: Health ministry efforts for early practical use of COVID-19 vaccines⁶⁸



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Although they remain well behind their global competitors, Japan's major pharmaceutical firms are proceeding with domestic development of COVID-19 vaccines. On August 7, the health ministry chose six companies including Shionogi Co., Takeda Pharmaceutical Co. and Daiichi Sankyo Co. (out of the nine companies that applied) in the first round of public solicitation for an "emergency project to improve the vaccine production system" designed for promptly establishing a system for large-scale production of biopharmaceuticals including COVID-19 vaccines. Various measures have been taken⁷⁰ to promote an early supply of the vaccines in Japan, including distribution of some ¥90 billion in grants⁶⁹ to the selected firms through the Pharmaceutical Development Support Center.

Table 3 shows the situation of COVID-19 vaccine development in Japan.

Table 3: Status of COVID-19 vaccine development in Japan (major projects, as of August 21, 2020)⁷¹

	Basic information	Status	Target (Timing based on hearing of developers)	Prospect of production
Shionogi National Institute of Infectious Diseases (NIID)/ UMN Pharma *Recombinant protection vaccine	The virus' protein (antigen) produced through gene recombination technology and then administered to humans	Animal tests for evaluate efficacy underway	Intends to start clinical tests by the end of 2020 at the earliest	Aims to produce vaccine enough for 30 million people by the end of 2021; Subsidies of ¥22.3 billion provided under the project to improve the vaccine production system
Daiichi Sankyo Institute of Medical Science, the University of Tokyo *mRNA vaccine	The virus' messenger RNA administered to humans. The virus' protein (antigen) produced in human bodies.	The rise of antibody valence against the novel coronavirus confirmed in animal tests	Aims to start clinical tests in March 2021 at the earliest	¥6.09 billion in subsidies given under the project to improve the vaccine production system.
AnGes Osaka University/ Takara Bio *DNA vaccine	The virus' DNA administered to humans and its protein (antigen) produced from DNA via mRNA in human bodies	The Phase I and II clinical trial study tests already started		Takara Bio and Kaneka planning to produce the vaccine; Subsidies of ¥9.38 billion provided under the project to improve the vaccine production system

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<p>KM Biologics Institute of Medical Science, the University of Tokyo/ NIID/ National Institute of Biomedical Innovation, Health and Nutrition</p> <p>*Inactivated vaccine</p>	<p>A conventional type vaccine with inactivated virus to be administered to humans</p>	<p>Animal tests to evaluate efficacy underway</p>	<p>Aims to start clinical tests in November 2020 at the earliest</p>	<p>Subsidies of ¥6.03 billion given under the project to improve the vaccine production system</p>
<p>ID Pharma NIID</p> <p>*Virus vector vaccine</p>	<p>Genetic information of the novel coronavirus put on Sendai virus (hemagglutinating virus of Japan) and this virus administered to humans through the nose or through injection as a vaccine; The virus' protection (antigen) synthesized in human bodies.</p>	<p>Animal tests to evaluate efficacy underway</p>	<p>Aims to start clinical tests in March 2021 at the earliest</p>	

3.3. Japanese government's efforts to secure vaccines and international cooperation

3.3.1. Securing vaccines from Pfizer and AstraZeneca

As domestic development of COVID-19 vaccines made little progress, the Japanese government explored ways to secure vaccines through supply from overseas pharmaceutical companies for inoculation in Japan. On July 31, the health ministry announced that it had reached a basic agreement with Pfizer of the U.S. to receive a supply of vaccines adequate for 60 million people by the end of June 2021 if the firm succeeded in developing a vaccine for COVID-19.⁷³ On August 7, the health ministry said it had concluded a basic agreement with AstraZeneca to obtain a supply of vaccine adequate for 120 million inoculations from the beginning of 2021 (with vaccines for 30 million inoculations to be supplied in the first quarter) if the firm successfully developed a novel coronavirus vaccine.⁷⁴ These agreements with Pfizer and AstraZeneca covered basic conditions such as the volume of supply, and the government would proceed with further negotiations for final agreements.

The Foreign Ministry, the health ministry and the National Security Secretariat worked together in negotiating with the overseas pharmaceutical companies. In reality, however, the health ministry was not so positive about going through the Foreign Ministry's diplomatic channel.⁷⁵ A senior Foreign Ministry official said that since securing the vaccines was primarily the health ministry's job, the Foreign Ministry was not involved as an organization in the negotiations, especially the talks with Pfizer, and that the health ministry did not share much more information than was publicly disclosed.⁷⁶ On the other hand, concerning negotiations with AstraZeneca, Foreign Minister Motegi visited Britain in early August and held a dinner with his British counterpart Dominic Raab on the evening of August 5. Since Motegi exchanged words with Raab over the supply of vaccines, the August 7 announcement on the agreement with AstraZeneca was not unrelated to such diplomatic moves, the official said.⁷⁷

Meanwhile, a health ministry official said the Prime Minister's Office did not appear to have a firm grasp of the problems related to securing the vaccines.⁷⁸ It was not clear to what extent the National Security Secretariat functioned as the command tower in the negotiations to secure a supply of vaccines.⁷⁹ Another high-ranking Foreign Ministry official commented that since securing the supply of vaccines was essentially a matter that required a commitment by Japan's entire government, some body should have commanded the whole operation and better used the nation's diplomatic resources, instead of letting the health ministry alone take charge.⁸⁰

Various studies are also underway as to inoculations of vaccines. Concerning possible health damage from vaccination, the "basic policy on inoculation of vaccines against a new type (A/H1N1) of influenza" (December 2009)⁸¹ stipulated that the

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government could compensate for losses that manufacturers and distributors might suffer due to possible health damage from the use of vaccines imported to secure a supply for domestic inoculations, based on the special law on relief for health damage from the preventive inoculation against new-type influenza. At an August 21 meeting of the government's Novel Coronavirus Disease Control Subcommittee, possible relief measures against health damage from inoculations of COVID-19 vaccine, including compensation for the businesses involved, were discussed on the basis of the 2009 basic policy. Later, on August 28, the government's COVID-19 headquarters decided that "a necessary infrastructure should be created to ensure smooth vaccination of the people, including a system enabling people to be inoculated in their communities under the government's leadership, as well as appropriate relief measures in case health damage occurs" and that "the government should take legal steps prior to the start of inoculation so that it could make up for losses manufacturers and distributors suffered from paying compensation for health damage caused by the use of vaccines." The government thus confirmed its plan to proceed with improving the domestic system of vaccination.

3.3.2. International cooperation for securing vaccines

The governments of not only Japan but many other, mainly advanced, countries have taken steps to secure vaccines to inoculate their people through negotiations with major pharmaceutical firms. As of August 2, the United States had managed to secure vaccines for 700 million inoculations, Britain 250 million, the member countries of the European Union 700 million and Japan 490 million. On the other hand, concern has also been expressed over the competition to procure vaccines. According to a Bloomberg report, global vaccine production through the January-March period of 2022 was estimated to be just enough for 1 billion shots at most – falling short of the quantity reportedly secured in advance by Japan, the U.S. and Europe combined (1.3 billion shots).

Meanwhile, in late April, the WHO decided to set up Access to COVID-19 Tool Accelerator, a framework for international cooperation to develop new methods related to four fields that are important in combatting the novel coronavirus – diagnosis, treatment, vaccines and strengthening of public health systems – and to accelerate production and equal access. It also decided to co-lead COVAX, a mechanism to distribute vaccines to the people of the world in an equitable manner, together with the Coalition for Epidemic Preparedness Innovations (CEPI) and GAVI (the Global Alliance for Vaccines and Immunization). COVAX will select vaccines to be supplied and promises to supply vaccines enough for 20 percent of the participating countries' population. So far 78 countries have shown an interest in joining COVAX. Japan has taken part in it from the initial stages of the scheme.

Keizo Takemi, an Upper House member of the Liberal Democratic Party, said that Japan should search for a role that a middle-power country could play in the new

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global governance system while not only taking part in it as a Friend of COVAX, but also making steady financial contribution to the effort.⁸² A high-ranking Foreign Ministry official said that COVAX, a framework for multilateral cooperation, was very important as the international community undertakes the task of securing vaccines, and that Japan needs to play a certain role in the international cooperation toward that goal.⁸³ Although the Japanese government has already concluded basic agreements with several firms on vaccine supply, the COVAX facility can serve as yet another means for Japan to secure vaccines. Japan is actively engaging in discussions at COVAX since it is a venue in which the nation can contribute to equitable international distribution of vaccines.⁸⁴

Notes

1. The Health, Labor and Welfare Ministry, “Reference material No. 1: The current situation of and prospects for the pharmaceutical industry”
<https://www.mhlw.go.jp/content/10801000/000398096.pdf>
2. GCP is a standard determined by the health ministry’s ordinance under the Pharmaceutical Affairs Law and is strictly applied.
3. The health ministry, “Rules for clinical trial study (GCP)”
<https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/>
4. Chiba Medical Center of National Hospital Organization, “Clinical Trial Study Control Division. For ordinary citizens. The process of how a new drug comes into being”
<https://chiba.hosp.go.jp/ir-ken-chi-new.html>
5. Generic drugs are being sold to compete with these drugs. Because the latter’s prices under the nation’s public health insurance system have been lowered in stages, profit from their sales tends to decrease gradually.
6. The health ministry, “Reference material. Material submitted by the Health, Labor and Welfare Ministry in November 2019”
<https://www.mhlw.go.jp/content/10807000/000567934.pdf>
7. CEPI is a partnership between the government sector and the private sector established in the January 2017 World Economic Forum annual meeting in Davos, Switzerland, to promote development of vaccines through global cooperation. In addition to Japan, Norway, Germany, Britain, Australia, Canada and Belgium, Bill and Melinda Gates Foundation and the Wellcome Trust are providing funds. In ordinary times, it aims to promote development of low-demand vaccines against such diseases as Ebola hemorrhagic fever (EHF) that are in danger of spreading worldwide and to supply vaccines with accessible prices to low- and middle-income countries where the possibility of spread of such diseases is high.
8. Inovio Pharmaceuticals of the U.S., the University of Queensland, Australia, Moderna of the U.S. and the National Institute of Allergy and Infectious Diseases of the U.S. (NIAID)
9. Material released by the health ministry, “We will push the development of vaccines” (January 24, 2020)
https://www.mhlw.go.jp/stf/newpage_09087.html
10. The Japanese Association for Infectious Diseases, “How to consider using antiviral drugs in treatment of COVID-19? The first edition.” (February 26, 2020)
http://www.kansensho.or.jp/uploads/files/topics/2019ncov/covid19_antiviral_drug_200227.pdf
11. Observational study: A series of research activities to accumulate and analyze treatment results and other data concerning medical practice in which drugs are administered for treatment of diseases for whose treatment they are not originally intended after obtaining the consent of patients following the procedure set down by the ethics committee and other bodies of a medical institution.
12. The Expert Meeting on the Novel Coronavirus Disease Control, “Situation analysis and recommendations on COVID-19 measures” (June 5, 2020)

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- https://www.kantei.go.jp/jp/singi/novel_coronavirus/senmonkakaigi/sidai_r020529_2.pdf
13. Out of this amount, the health ministry provided ¥10.6 billion for CEPI and the Foreign Ministry ¥11 billion for The Global Alliance for Vaccines and Immunization (GAVI).
 14. The Office of Healthcare Policy of the Cabinet Secretariat, “The situation of support for developing medicines, etc. for novel coronavirus” (June 5, 2020)
<http://www.kantei.go.jp/jp/singi/kenkouiryou/sanyokaigou/dai19/sankou2.pdf>
 15. Gilead Sciences, Inc., “Gilead Sciences has started two Phase III tests using Remdesivir which it is developing as an antiviral curative drug for COVID-19”
https://www.gilead.co.jp/-/media/japan/pdfs/press-releases/02-27-2020/remdesivir-covid-19-trials_200227.pdf?la=ja-jp&hash=F910B49F73E16D0AF34399978BD1CA96
 16. Gilead Sciences, Inc., “Gilead Sciences, Inc. announced data on 53 patients who were subject to the humanitarian use of the antiviral drug Remdesivir, which the company is developing, in The New England Journal of Medicine” (April 10, 2020)
https://www.gilead.co.jp/-/media/japan/pdfs/press-releases/04-13-2020/nejm_2020410.pdf?la=ja-jp&hash=AFF6A91D2334AB0CD5D9EFD62D5048D3
 17. <https://www.afpbb.com/articles/-/3280993>
 18. Beigel JH, et al. Remdesivir for the Treatment of Covid-19 – Preliminary Report. N Engl J Med. 2020 May 22;NEJMoa2007764. doi: 10.1056/NEJMoa2007764.
 19. The health ministry’s COVID-19 headquarters, “On grasping the appropriate amount of Remdesivir for its use for serious cases and other matters in measures to counter the novel coronavirus (request)” (May 4, 2020)
https://www.jsicm.org/news/upload/mhlw_200504_02.pdf
 20. EUA is a temporary measure and does not replace submission of official application forms or the process of screening and approval. It allows supply and emergency use of Remdesivir for treatment of the novel coronavirus infectious disease.
 21. Gilead Sciences, Inc., “Gilead Sciences has obtained Emergency Use Authorizations from the U.S. Food and Drug Administration for the use of the antiviral drug Remdesivir, which is in the stage of development, as a curative medicine for COVID-19” (May 20, 2020)
https://www.gilead.co.jp/-/media/japan/pdfs/press-releases/05-02-2020/remdesivir_eua_release.pdf?la=ja-jp&hash=36E9F5D91CD7485782A048A36341BCE7
 22. The health ministry’s COVID-19 headquarters, “On grasping the appropriate amount of Remdesivir for its use for serious cases and other matters in measures to counter the novel coronavirus (request)” (May 4, 2020)
https://www.jsicm.org/news/upload/mhlw_200504_02.pdf
https://www.jsicm.org/news/upload/mhlw_200504_01.pdf
 23. Clause 1 of the Article 14-3 of the law on securing the quality, effectiveness and safety of medical drugs and medical instruments and other related matters, provides a system to grant special approval to a drug that meets the following conditions. In such a case, other documents than the results of clinical tests can be submitted after approval is granted. The conditions are: 1) there is a need for emergency use of the drug to prevent the spread of a disease; 2) no appropriate means are available except the use of the drug in question; and 3) the sale of the drug and related matters are approved abroad.
 24. Patients with serious conditions are defined as “serious cases whose oxygen saturation rate is 94 percent or less (room air), or who need oxygen inhalation, or for whom extracorporeal membrane oxygenation or ECMO was introduced, or who require invasive artificial respiration management.” “VEKLURY intravenous drip injection solution 100mg/VEKLURY intravenous drip injection use 100 mg, prepared in May 2020 (the first edition), 5. Caution concerning the efficacy or effects.”
https://www.info.pmda.go.jp/go/pack/62504A3A1029_1_02/
 25. The Pharmaceutical Evaluation Division of the Pharmaceutical Safety and Environmental Health Bureau, the health ministry, “On the special approval of Remdesivir pharmaceuticals on the basis of the law on securing the quality, effectiveness and safety of medical drugs and medical instruments and other related matters” (May 7, 2020)
<https://www.mhlw.go.jp/content/000628076.pdf>
 26. The second medical drugs division of the Pharmaceutical Affairs and Food Sanitation Council, “The

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- May 7, 2020 meeting minutes of the Second Medical Drugs Division of the Pharmaceutical Affairs and Food Sanitation Council”
https://www.mhlw.go.jp/stf/newpage_12439.html
27. This is an ordinary medicine for influenza that has already received approval. It is sold under the trade name of Tamiflu by Roche (F. Hoffmann-La Roche, Ltd.) of Switzerland.
 28. “Anti-influenza virus drug Avigan pills 200mg. Revised in April 2019 (7th edition)”
http://fftc.fujifilm.co.jp/med/abigan/pack/pdf/abigan_package_01.pdf
 29. The Japanese Association for Infectious Diseases, “How to consider anti-viral drug-based treatment of COVID-19? The first edition. (February 26, 2020)”
http://www.kansensho.or.jp/uploads/files/topics/2019ncov/covid19_antiviral_drug_200227.pdf
 30. Interviews with health ministry officials
 31. Fujifilm Toyama Chemical Co., “Anti-influenza virus drug Avigan pills. An announcement on a domestic Phase III clinical test intended for patients of the novel coronavirus disease and the production system” (March 31, 2020)
https://www.fujifilm.com/jp/ja/news/list/3210?_ga=2.169764449.1544869722.1596760118-972541912.1596760118
 32. Diethyl malonate is an organic compound used as a raw material for such products as synthetic aromatics, farm chemicals and medical drugs. It is also a raw material for Avigan.
 33. Denka Co. is the only domestic manufacturer of diethyl malonate and Denka Co., an affiliate of Denka, is the only domestic manufacturer of monochloroacetic acid, which is a raw material for diethyl malonate. Within its group, Denka produced diethyl malonate under an integrated production system whose products ranged from raw materials to final products until April 2017. (Denka Co., “An announcement concerning supply of raw materials for Avigan,” April 2, 2020)
https://www.denka.co.jp/storage/news/pdf/714/20200402_denka_supply_dem.pdf
 34. On June 1, in response to the government’s request, Denka Co. started shipment of diethyl malonate, a raw material for Avigan, in an attempt to expand the stockpiles of Avigan to a level adequate enough for use for 2 million people, a goal set by the government as part of its emergency economic countermeasures.
 35. The Japanese Association for Infectious Diseases, “COVID-19 pneumonia cases whose conditions were found to have rapidly improved and which were found to have turned to negative in PCR tests thanks to the use of Favipiravir (Avigan)” (April 6, 2020)
http://www.kansensho.or.jp/uploads/files/topics/2019ncov/covid19_casereport_200409_1.pdf
 36. The calculation result was obtained on the basis of the method of how to administer Favipiravir (1,800 mg each time, twice the first day; 800 mg each time, twice the second and the following days. Maximum 14 days), which is based on the Japanese Association for Infectious Diseases’ “How to consider anti-viral drug-based treatment of COVID-19?”
 37. Fujifilm Holdings Corp., “Expansion of production of the anti-influenza virus drug Avigan tablets for treatment of the novel coronavirus disease” (April 15, 2020)
https://www.fujifilm.com/jp/ja/news/list/3245?_ga=2.169764449.1544869722.1596760118-972541912.1596760118
 38. An interview with a staff member in the Prime Minister’s Office
 39. Concerning this move, a high-ranking official of the Cabinet Secretariat said, “The Prime Minister’s Office is doing everything on the premise that the results of the clinical trial study will be OK,” giving an impression that “the Prime Minister’s Office is much too enthusiastic about Avigan.”
 40. Interview with a high-ranking health ministry official
 41. Fujita Health University “On the final report on the special clinical study of Favipiravir (Avigan)” (July 10, 2020)
<https://www.fujita-hu.ac.jp/news/j93sdv0000006eya.html>
 42. Interview with a high-ranking health ministry official
 43. On May 1, it was announced that for each country, Avigan would be provided in an amount adequate enough for administration to 20 patients in principle and 100 patients at most.
 44. An interview with a senior Cabinet Secretariat official
 45. An interview with a senior Cabinet Secretariat official
 46. The World Health Organization had not approved of distributing drugs that had not received minimum-

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- level domestic approval through the WHO and other international organizations.
47. Interview with an official at the Foreign Ministry
 48. The Cabinet Secretariat's Office for Pandemic Influenza and New Infectious Diseases Preparedness and Response, "The government's action plan to counter the new type of influenza and other diseases" (June 7, 2013 and updated on September 12, 2018)
http://www.cas.go.jp/jp/seisaku/ful/keikaku/pdf/h29_koudou.pdf
 49. The government's headquarters to cope with novel influenza "Basic policy on vaccine inoculation for new-type influenza (A/H1N1)" (October 1, 2010)
<https://www.mhlw.go.jp/kinkyu/kenkou/influenza/hourei/2009/12/dl/info1221-01.pdf>
 50. The health ministry's headquarters on novel influenza "On details of the countermeasures against the new-type influenza (A/H1N1) ~ Vaccines" (May 19, 2010)
<https://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou04/dl/infu100519-19.pdf>
 51. The report of the review meeting on measures against new-type influenza (A/H1N1)(June 10, 2010)
<https://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou04/dl/infu100610-00.pdf>
 52. The panel of experts on new-type influenza "The record of the 13th meeting of the panel of experts on new-type influenza. Opinions to be reflected in the proposals and action plan of the review meeting on measures against new-type influenza (A/H1N1) (draft)" (November 29, 2010)
<https://www.mhlw.go.jp/stf/shingi/2r9852000000xih0.html>
 53. Points in revising "the action plan for countermeasures against new-type influenza"
<https://www.mhlw.go.jp/stf/shingi/2r9852000001ryfy-att/2r9852000001ryn2.pdf>
 54. Interview with a high-ranking health ministry official
 55. <https://bio.nikkeibp.co.jp/atcl/news/p1/20/05/06/06888/>
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