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PERSPECTIVE

Conditional early approval for new drug applications in Japan: Current and emerging issues

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The conditional approval for a new drug application in Japan is an expedited drug development program intended to improve patients' access to potentially effective drugs in serious diseases without effective therapies, particularly where timely confirmatory clinical trials are difficult to conduct. Several new drugs have been approved through this pathway, however, there are emerging issues to be addressed. This paper provides an overview of current state and future directions of conditional approval in Japan.

As have many regulatory agencies in high-income countries, the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the Pharmaceuticals and Medical Devices Agency (PMDA)/Ministry of Health, Labour and Welfare (MHLW) in Japan have implemented expedited programs to improve patients' access to innovative new drugs for serious diseases without effective therapies. The FDA's accelerated approval (AA) and the EMA's conditional marketing authorization (CMA) were introduced in 1992 and 2006, respectively,[1,2] whereas the PMDA/MHLW's conditional early approval (CEA) program was established in 2017.[3] These programs provide early access to possible effective treatments for patients with serious or life-threatening diseases, but there are some differences in their eligibility criteria, requirements/conditions, and its use/availability.

The CEA program is designed to improve the consistency and predictability of regulatory interactions with sponsors to facilitate patients' access to new drugs.[3] To be eligible for this program, a product must be intended to treat a serious disease, offer superior clinical utility compared to existing treatments, and has demonstrated in clinical trials a certain level evidence reasonably predictive of efficacy and safety. The CEA is granted with a condition of conducting postmarketing surveillance or other studies to demonstrate the efficacy and safety of the drug. However, the MHLW's notification for CEA does not clearly state the possibility of revoking approval if efficacy cannot be demonstrated in the postmarketing studies.

The FDA's AA is a program to facilitate the expedited approval of drugs that treat serious conditions and address unmet medical needs.[1] To qualify for AA, a drug must be intended to treat a serious or life-threatening disease and offer potentially meaningful therapeutic advantage over existing treatments. The AA is granted based on a demonstrated effect on either an unvalidated surrogate endpoint, which is a measure that is thought to predict clinical benefit but is not itself a measure of clinical benefit, or an intermediate clinical end point, which is a measure of a therapeutic effect that is considered reasonably likely to predict the clinical benefit of a drug, such as an effect on irreversible morbidity and mortality. After marketing approval, postmarketing or ongoing studies are generally

required to demonstrate the clinical benefit of the drugs. The FDA has a legal authority to withdraw the product from the market if the clinical benefit is not demonstrated during postmarketing studies, or such studies have not been completed in a timely manner.[1] However, there are several challenges and limitations, including limited evidence and inadequate labeling, delayed or incomplete postmarketing studies, and market access/cost issues, and it is not easy to revoke an approval once it has been granted. Despite these challenges/limitations, the use of the AA program has been continuously increasing for both oncology[4] and non-oncology drugs[5] in recent decades.

The EMA's CMA is a program that allows for the expedited approval of drugs in the European Union based on the data demonstrating the potential benefits of the medicine outweighing its risks.[2] The CMA is granted to medicines that address unmet medical needs and offer significant benefits to patients who currently have limited treatment options. It makes the drugs to be available to patients in the European Union while additional data are collected. The CMA is valid for 1 year, and it can be renewed annually, subject to additional data being provided to support the product's continued benefit-risk balance. The AA and CMA can be converted to a full approval after sufficient data on its efficacy and safety is obtained. Among 278 indications granted AA in the United States, 139 were converted to full approval and 28 were withdrawn between 1992 to 2021, whereas 24 of 72 medicines granted CMA in the European Union were converted to a full marketing authorization between 2006 and 2021.

The proportion of the CEA for new molecular entity (NME) drugs, including biologics for human use approved in Japan, was compared to that of the AA/CMA for those approved in the United States/European Union between 2017 and 2021 (Figure 1a). Detailed information on approved drugs is collected from the websites and review reports of the regulatory agencies.[2,6,7] During 5 years, only four (2.1%) of 189 NMEs were granted the CEA in Japan, whereas 45 (17.8%) of 256 NME and 38 (19.0%) of 200 NMEs were granted the AA in the United States and the CMA in the European Union, respectively. Although the difference in the number of NMEs between Japan and the United States/European Union became smaller, the gap between the CEA and the AA/CMA use has widened over the years. The PMDA/MHLW granted the CEA based on small-scale, uncontrolled studies using an unvalidated surrogate end point as a primary end point and requested postmarketing surveillance for all these drugs (Table 1). As a specific condition for those, except lorlatinib, the PMDA/MHLW requested sponsors to publish information or submit data on the results of a planned phase III randomized study using a clinical end point. However, the PMDA/MHLW's review reports do not mention that they will review the results of those randomized studies and may revoke an approval if efficacy is not demonstrated.

Our analysis showed that the CEA in Japan has been used only a few new drugs compared to the AA/CMA in the United States/European Union. The lack of use of the CEA in Japan is probably due to the following reasons. First, the CEA is no longer different from the full approval process except for its uncertain efficacy (Figure 1b). The postmarketing surveillance as a condition of the CEA is generally required for the full approval in Japan. Further, there are no expiration dates or significant marketing conditions for CEA-approved drugs, so that the sponsors do not need to apply for full approval after getting the CEA. Second, the PMDA/MHLW rarely revokes the approval of a new drug once it has been granted, because it is difficult to determine that the efficacy of the drug is not sufficient through postmarketing surveillance as a single arm observational study. These factors may lead the PMDA/MHLW not to use the CEA program in drug development in Japan.

Drug lag has been a critical issue of public health in Japan for many years.[8] Drug lag refers to the time it takes for a new drug to be developed, tested, and approved for use in clinical practice in comparison to the time it takes to do so in another jurisdiction. Many factors contribute to drug lag, including the time it takes to complete clinical trials, the regulatory approval process including when the marketing application is filed with the comparative authorities and the various regulatory pathways used, and the cost of developing and producing new drugs. The clinical significance of drug lag is that it can impact patient outcomes by delaying access to new and potentially more effective treatments.

Global clinical trials provide an opportunity for simultaneous drug development and contribute to reducing drug lag. However, there has recently been an increase in the number of global clinical trials in which a new drug application under the AA/CMA program is filed with the FDA/EMA based on the results of an analysis using unvalidated surrogate end points, and the full approval is filed based on the results of the final analysis (Figure 1c).[9] If Japan were to adopt only the full approval without using the CEA program, it would exacerbate drug lag due to differences in the policies of regulatory agencies. We found that most new drugs under the AA/CMA program in the United States/European Union have been authorized through a standard full approval process in Japan. AA/CMA can be granted before clinical trials are completed and full approval granted in Japan. Although various expedited programs have been recently introduced by regulatory agencies to improve patients' access to innovative new drugs, it is necessary for regulatory agencies to engage in discussions and debate on the most effective expedited drug development program for patients to fully

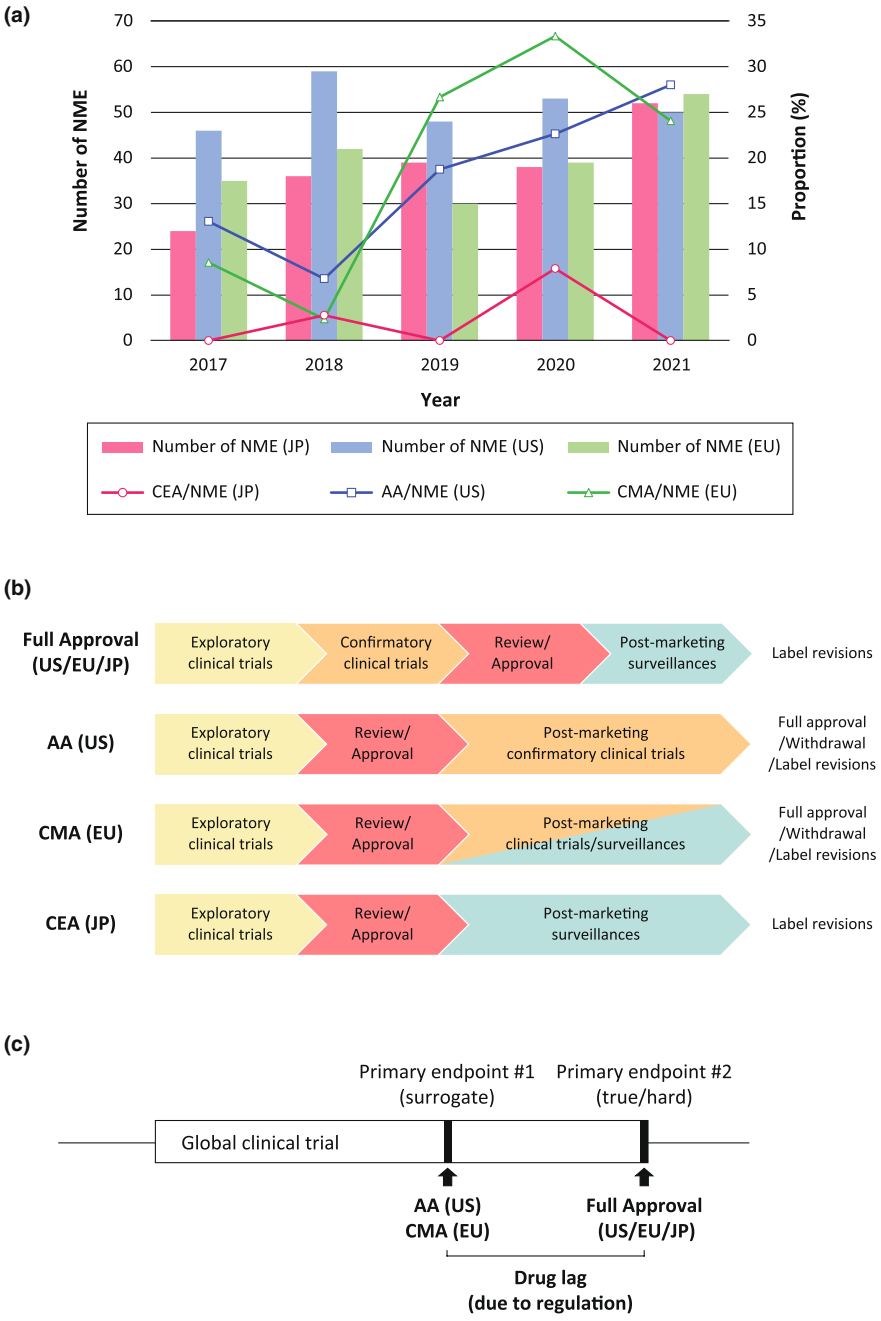

FIGURE 1 Conditional early approval in Japan, accelerated approval in the United States, and conditional marketing authorization in the European Union. (a) NME granted the CEA in Japan and those granted the AA/CMA in the United States/European Union between 2017 and 2021. The proportion of the AA/CMA for NME in the United States/European Union has increased recently, whereas that of the CEA in Japan remains low. The difference in the number of NME between Japan and the United States/European Union became small. (b) Scheme of the CEA in Japan and the AA/CMA in the United States/European Union. The CEA/AA/CMA may be granted based on small-scale, dose-finding clinical studies investigating drug efficacy and safety using a surrogate endpoint. The PMDA/MHLW requests postmarketing surveillance when granting the CEA. The FDA requests postmarketing clinical trials when granting the AA and sometimes revokes approval if the trials do not provide evidence of clinical benefits. The EMA request additional postmarketing data, which can include clinical trial results as well as postmarketing surveillance studies. The CMA is valid for 1 year and can be renewed annually. (c) The gap of use of the CEA and the AA/CMA results in drug lag due to differences in the policies of regulatory agencies. There is an increase in drug development strategy in which a new drug application under the AA/CMA program is filed with the FDA/EMA based on the results of an interim analysis using surrogate end points, and the full approval is filed based on the results of the final analysis of global clinical trials. AA, accelerated approval; CEA, conditional early approval; CMA, conditional marketing authorization; EMA, the European Medicines Agency; EU, European Union; FDA, the US Food and Drug Administration; JP, Japan; MHLW, the Ministry of Health, Labour and Welfare; NME, new molecular entity; PMDA, the Pharmaceuticals and Medical Devices Agency; US, United States.

TABLE 1 Drugs granted conditional early approval in Japan from 2017 to 2021.

Approval dates	Approval category	Generic name (Brand Name)	Sponsor	Indication	Submitted studies	Approval condition	US/EU approval
September 21, 2018	New molecular entity	Lorlatinib (Lorbrena)	Pfizer	Unresectable or recurrent ALK-positive non-small cell lung cancer with resistance or intolerance to ALK tyrosine kinase inhibitors	A phase I/II, multi-regional, uncontrolled study with a primary end point of the overall response rate	Postmarketing surveillance	US: AA > Full approval EU: CMA
December 21, 2018	New indication	Pembrolizumab (Keytruda)	MSD/Merck	Unresectable or metastatic, MSI-high or mismatch repair deficient solid tumor	Two phase II, multi-regional, uncontrolled studies with a primary end point of the overall response rate	Postmarketing surveillance; Provision to the public of long-term results of submitted phase II studies	US: AA > Full approval EU: Full approval
March 25, 2020	New molecular entity	Trastuzumab deruxtecan (Enhertu)	Daiichi-Sankyo	Unresectable or recurrent HER2-positive breast cancer in patients who have previously been treated with chemotherapy (for use only if refractory or intolerant to standard therapies)	A phase I, multiregional, uncontrolled study with a primary end point of the overall response rate; A phase II, multiregional, uncontrolled study with a primary end point of the overall response rate	Postmarketing surveillance; Provision to the public of results of a planned phase III, multiregional, double-blinded, placebo-controlled, randomized study with a primary end point of progression-free survival	US: AA EU: CMA
March 25, 2020	New molecular entity	Viltolarsen (Viltepso)	Nippon-Shinyaku	Duchenne muscular dystrophy with a confirmed deficiency of the dystrophin gene amenable to exon 53 skipping therapy	A phase I/II, uncontrolled study in Japan with a primary end point of expression of dystrophin protein; A phase II, double-blinded, placebo-controlled, randomized study outside Japan with a primary end point of expression of dystrophin protein	Postmarketing surveillance; Submission of a planned phase III, multiregional, double-blinded, placebo-controlled, randomized study with a primary end point of change in time to stand	US: AA EU: Not yet
September 25, 2020	New molecular entity	Cetuximab sarotalocan sodium (Akalux)	Rakuten Medical	Unresectable locally advanced or recurrent head and neck cancer	A phase I, uncontrolled study in Japan with a primary end point of the overall response rate; A phase I/IIa, uncontrolled study outside Japan with a primary end point of the overall response rate	Postmarketing surveillance; Provision to public of results of a planned phase III, multiregional, open-label, randomized study with a primary end point of progression-free survival	US: Not yet EU: Not yet

Abbreviations: AA, accelerated approval; ALK, anaplastic lymphoma kinase; CMA, conditional marketing authorization; HER2, human epidermal growth factor receptor 2; EU, European Union; MSI, microsatellite instability; US, United States.

benefit from global clinical trials and achieve greater regulatory alignment.

To improve the effectiveness of the CEA for facilitating new drug development, several changes may need to be considered:

1. Making the eligibility criteria of the CEA program more compatible with that of the AA/CMA and promoting CEA approvals for drugs authorized under the AA/CMA program.
2. Implementing an expiration date for CEA approvals similar to the CMA. This would ensure that the efficacy and safety of CEA-approved drugs are regularly re-assessed.
3. Requiring postmarketing studies to demonstrate the efficacy and safety of CEA-approved drugs, similar to the system used by AA.
4. Revoking approval for drugs that do not demonstrate clinical benefits in these postmarketing studies, also similar to the AA's approach.

The approval process for pharmaceuticals and other products often involves balancing the need to ensure efficacy and safety of a medical product with the known negative public and personal health impacts of a serious disease with no effective treatments. However, excessive deregulation in the name of rapid general availability of a medicine can compromise patient safety and increase the risk of harm from drugs. This is a complex issue that needs to be approached from the perspectives of patients, companies, public health, and regulatory agencies. It is hoped that by making these changes, the CEA program in Japan will function more efficiently and improve access to possibly effective drugs when patients have serious diseases for which there is no effective therapy.

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