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ORIGINAL RESEARCH

A Qualitative Interview Study on Expanded Access Clinical Trials for Compassionate Use in Japan

Haruto Hayashi[1], Takehide Nogita[2,3], Hideki Maeda[1,2]

[1]Department of Regulatory Science, Faculty of Pharmacy, Meiji Pharmaceutical University, Tokyo, Japan; [2]Department of Regulatory Science, Graduate School of Pharmaceutical Science, Meiji Pharmaceutical University, Tokyo, Japan; [3]CMIC Co Ltd., Tokyo, Japan

Correspondence: Hideki Maeda, Department of Regulatory Science, Faculty of Pharmacy, Meiji Pharmaceutical University, 2-522-1, Noshio, Kiyose-city, Tokyo, 204-5255, Japan, Tel/Fax +81-42-495-8952, Email maeda@my-pharm.ac.jp

Purpose: An expanded access clinical trials (EACTs) provides exceptional patient access to investigational new drugs for life-threatening diseases for which no effective treatment exists. Based on public information, we have studied EACTs since 2016, when the EACT system was launched in Japan. In this study, we investigated the reality of EACTs by interviewing pharmaceutical companies and clarifying how they view them.

Patients and Methods: We conducted semi-structured interviews with 10 pharmaceutical companies developing new drugs. This study aims to clarify the status of EACTs, so we selected pharmaceutical companies that develop innovative drugs for which they may perform EACTs (however, experience in conducting EACTs was optional).

Results: All those surveyed were aware of EACTs. Twelve access clinical trials were conducted, and the EACT implementation rate for pivotal clinical trials was 2.5%. The most common reason for implementing an EACT was "requests from physicians and medical institutions" (nine companies, 90.0%), and the most common reason for not implementing an EACT was "the applicability of the system" (five companies). Improvements to EACTs were identified by eight companies (80.0%); financial assistance by six companies (60.0%); reducing the scope of data to be collected and simplifying the procedure by six companies (60.0%). Seven companies (70.0%) responded that a Single Patient Investigational New Drug Application should be conducted, suggesting that the system should be revised.

Conclusion: An interview survey of ten pharmaceutical companies developing new drugs in Japan regarding expanded access clinical trials indicated that there were issues with the system. Many wished to improve the system by establishing a single patient access system, supporting resources, and simplifying procedures. Based on our interviews with 10 Japanese pharmaceutical companies, it was found that the system needed to be improved by introducing a single patient access system, providing supporting resources, and simplifying procedures. In Japan, about eight years have passed since EACT was established, and it appears a revision of the EACT legislation is due.

Keywords: clinical trials, investigational new drugs, patient access, semi-structured interview

Introduction

Drug development takes longer than ten years, from the discovery of a drug candidate as a compound to conducting nonclinical and clinical trials, receiving approval from local regulatory authorities, and being marketed as a product.[1] However, the early provision of effective treatments for patients suffering from fatal diseases is urgent and socially significant. Various measures have been implemented to speed up the delivery of innovative new drugs to patients, including increased development through orphan drug designation or SAKIGAKE designation and shorter review periods with priority review process or expedited review process.[2] One such initiative is compassionate use (CU).[3–6]

CU is an exceptional mechanism system that allows investigational new drugs to be trialed for therapeutic purposes from an ethical and humanitarian standpoint to treat life-threatening severe diseases for which no existing treatment is effective. CU has been institutionalized in Europe and the United States for a relatively long time. The US FDA implements CU using a system called the Expanded Access Program.[7,8] The FDA uses administrative terms such as

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"treatment use of an investigational new drug", "expanded access to unapproved therapies and diagnostics", and "expanded access", which it describes as the same as compassionate use that is being used in Europe.[9] The European Legislature created the regulatory framework[10] regarding CU in 2004, although CU is well established in France and Italy. This regulatory framework is described in Regulation No.EC726/2004, a superior law in the EU legal system.[11]

In Japan, CU was established in January 2016 as the Japanese version of the compassionate use program (J-CU program).[12] The J-CU program, was based on systems used in the US and Europe (EU). Before 2016, CU in Japan was an obscure system called "supply outside of a clinical trial", and drugs under investigation were obtained through personal import. In other words, before 2013, there was no legislation regarding CU, and investigational drugs were used in a gray area, so proper legislation was needed at that time. The application of CU began with the conduct of clinical trials named Expanded Access Clinical Trials (EACT), or "clinical trials conducted from a humanitarian perspective". The EACT system in Japan was also established to provide treatment for life-threatening diseases for which no existing therapeutic agent was effective. In Japan, the EACT was to be implemented under the standard clinical trial framework. In addition, so as not to affect the development of the drug concerned, the rules were designed so that the trial would be conducted after the inclusion of the pivotal clinical trial (PCT). Furthermore, expanded access to clinical trials was recommended for pharmaceuticals with high societal demands. The following conditions were set as conditions of high societal demand:

1. Drugs with an Expanded Access Program (Intermediate size Investigational New Drug (IND)/protocol) or Treatment IND/protocol in the US.
2. Products in the SAKIGAKE designation system. The SAKIGAKE designation system is one of Japan's expedited regulatory pathways to promote the development for innovative pharmaceuticals, medical devices, and regenerative medicines, similar to Breakthrough Therapy Designation in the US.
3. Orphan disease.
4. Drugs requested for development by the Review Committee on Unapproved Drugs because of their high medical need. The Japanese Review Committee on Unapproved Drugs was established in 2009. Its primary role is to eliminate drug approval delays between Japan and the US or EU, and the Committee promotes the granting of special expedited approval to address such drug lags.[13]

The implementation of EACT started in 2016. with a notification by the Japanese Ministry of Health, Labour and Welfare.[12] The title of the notification was "EACT from humanitarian perspective". About eight years have passed since EACT was introduced. We conducted a survey of EACT in Japan from 2016–2022.[14.] We investigated this study based on publicly available PMDA information, and we suggest that expanded access clinical trials are not always actively conducted and that there may be challenges in doing so. The study was based on publicly available PMDA information, and it was suggested that expanded access clinical trials are not always actively conducted and that there may be challenges in doing so. In this study, we conducted an interview survey of pharmaceutical companies that sponsor EACT and examined their awareness of EACT, how pharmaceutical companies conduct and perceive it, and information on issues related to EACT.

Materials and Methods

This study aims to clarify the status of EACT, so we selected pharmaceutical companies that are developing innovative drugs as pharmaceutical companies that may perform EACT (however, experience in conducting EACT was optional). Specifically, we approached and interviewed the members of the R&D Head Club (https://rdhead-club.com/), an organization comprising the heads of research and development departments of pharmaceutical companies engaged in the development of new drugs in Japan. Twenty companies were approached, 10 of which have responded. We employed the COREQ reporting guideline for our interviews.[15]

We used a written explanation to provide the details of the study to the participants individually. We obtained consent from the candidates to participate in the interview by e-mail after obtaining consent from those companies that provided their consent for the interview. We managed the information obtained according to laws and regulations such as the

Personal Information Protection Act. We did not include sensitive personal information in this study. We sent the questionnaires (Supplement File 1) before the interviews. Semi-structured interviews were conducted according to Braun and Clarke's method, which included participants' answers to the questions posed, background to their selection, and answers received other than the options provided in the questionnaires.[16] The interviews were recorded, transcribed, and tallied. The transcribed and tabulated information was presented to the interviewees and comments invited. The final results were tabulated based on the transcriptions, and figures and tables were created. Interviews were conducted from October 2022 to January 2023.

The questionnaire was developed by the authors based on public information from PMDA and previous studies.[14] The content of the questionnaire included the reasons for implementing EACT based on the interviewees' background information, the timing of considering EACT, Single Patient IND, and areas for improvement of EACT. The following is a summary of the results of the study.

This study was discussed and approved by the Meiji Pharmaceutical University Ethics Review Committee (Approval number: 20-0020).

Results

Background Information of the Interviewees

We approached 20 companies that belong to the R&D head club for interviews. Ten pharmaceutical companies and ten individuals agreed to respond. Amgen, Astellas, AstraZeneca, Chugai, Daiichi-Sankyo, Eli Lilly, GSK, Otsuka, Pfizer, and Sanofi were among the companies that responded. These companies' Japanese revenue as of FY2023 were $- (undetermined); $2,119,085,331; $2,677,781,657; $3,397,404,525; $4,048,278,224; $1,349,270,852; $1,662,716,714; $2,143,369,362; 1,932,830,149; and $1,349,270,852, respectively.[17] The reason provided for a lack of response, was—in most cases—that there was no department or manager to provide an appropriate response. We conducted twelve expanded access clinical trials. There were also 488 pivotal clinical trials. The expanded access clinical trial implementation rate for pivotal clinical trials was 2.5%. Table 1 shows the background of the interviewees and respondent companies. Eight respondents (80.0%) were affiliated

Table 1 Interviewee Background Information (n=10)

Item		Distribution
Age	Mean ±SD	50.2±6.75
	Median [25%:75%].	53 [45:57]
Sex	Male	7 (70.0%)
	Female	2 (20.0%)
	N/A	1 (10.0%)
Pharmaceutical industry Work history	Mean ±SD	23.7±5.67
	Median [25%:75%].	23 [19:28.5]
Current affiliation	Development	8 (80.0%)
	Medical affairs	1 (10.0%)
	Other	1 (10.0%)
Job title	General manager	1 (10.0%)
	Manager	5 (50.0%)
	Section Chiefs and Managers	2 (20.0%)
	N/A	1 (10.0%)

(*Continued*)

Table 1 (Continued).

Item		Distribution
Disease of interest	Cancer	10 (100.0%)
	Neurological disorder	5 (50.0%)
	Rare disease	3 (30.0%)
	Immunological area	3 (30.0%)
	Vaccine	2 (20.0%)
	Circulatory disease	2 (20.0%)
	Other	5 (50.0%)
Awareness of expanded access clinical trials	Yes	10 (100/0%)
	No	0 (0.0%)

Abbreviation: N/A, not applicable.

to the development divisions. Cancer was the highest-profile disease among the ten pharmaceutical companies that responded (100.0%), followed by neurological diseases for five companies (50.0%) and rare diseases and immunological areas for three companies (3.0%). All the companies reported awareness of EACT.

Reasons for Conducting EACT

Table 2 shows the results of the questionnaire on the stance on conducting EACT and the reasons for implementing it. Those falling under the SAKIGAKE designation system recommended conducting EACT. The use of EAP conduction in the US, orphan drugs, and requests from the authorities to implement it were further reasons. However, physicians and medical institutions required both the standard (stance) and the reasons for implementing EACT. Regarding the standard

Table 2 Stance and Reasons for Implementing Expanded Access Clinical Trials

Standards for implementing expanded access clinical trials (Stance)	Because it is subject to the SAKIGAKE designation system	2 (20.0%)
	Because EAP was implemented in the United States	3 (30.0%)
	Because the product is designated as an orphan drug	2 (20.0%)
	Because it was requested by the authorities	2 (20.0%)
	Because it was requested by physicians and medical institutions	9 (90.0%)
	Because it was requested by a patient	6 (60.0%)
	Other	2 (20.0%)
Reasons for the implementation	Because it is subject to the SAKIGAKE designation system	2 (16.7%)
	Because EAP was implemented in the United States	5 (41.7%)
	Because the product is designated as an orphan drug	1 (8.3%)
	Because it was requested by the authorities	0 (0.0%)
	Because it was requested by physicians and medical institutions	7 (58.3%)
	Because it was requested by a patient	3 (25.0%)
	Other	4 (33.3%)

for implementing EACT (stance), two (2.0%) companies were subjected to the SAKIGAKE designation system, three (30.0%) implemented EAP in the US, two (20.0%) implemented orphan drugs, and two companies (20.0%) were requested to do so by the authorities.

When to Consider EACT

Table 3 shows the results of the questionnaire on the stance toward implementing EACT and reasons for implementation. In terms of the stance of when to consider EACT, four companies (40.0%)—the highest number—had considered EACT prior to the start of PCT, while 0% had actually implemented EACTs prior to the start of PCT. Five companies (41.7%) actually implemented EACT after the start of the PCT, followed by four companies (33.3%) after the top-line results of PCT were published. One company responded, "In oncology, it is difficult to distinguish between phases, so we have not set a stance, such as filing an application if good results are obtained in Phase 1", while another company reported that, "In principle, we follow the SOP for EACT, so the timing varies between stance and practice".

Single Patient IND

In the US, there is a system similar to EACT on an individual basis (Single Patient IND) rather than a group basis. However, there is no single-patient basis EACT in Japan. Therefore, when interviewed about their opinions on the availability of EACT for individuals in Japan, seven companies (70.0%) mentioned that a Single Patient IND should be performed (Figure 1a), and six companies (60.0%) mentioned that they would conduct a Single Patient IND if they had one (Figure 1b). In this part, the author informed the interviewee of the characteristics of Single Patient IND in advance, and then interviewed the interviewee about the advantages and disadvantages of Single Patient IND in their opinion. As advantages, the interviewees responded, "It can provide options tailored to individual patients", "It can shorten the time to conduct an EACT", and "It increases the number of patients who can receive an EACT". The disadvantages mentioned included, "If there is no legal relaxation, there will be no time difference in implementation between Single Patient IND and EACT", "The more we do it, the more time and effort we have to devote to Single Patient IND and the cost of drugs", "We have to balance resources with companies that are commercial institutions", "The procedure will be more complicated", and "There will be more patients who can receive the EACTs. The more it is done, the more complicated the procedure will be, and the more the burden on medical institutions will increase".

Improvements to EACT

Table 4 shows the results of the survey on improvements to EACT. Regarding the points raised for improvement of EACT, financial assistance was the most common (eight companies, 80.0%), followed by reduction in the scope of data

Table 3 Stance on When to Consider Implementing an Expanded Access Clinical Trial and When It is Actually

(3) When to consider EACT (Stance)	Before the start of the main clinical trial	4 (40.0%)
	At the end of subject inclusion of the main clinical trial	2 (20.0%)
	After the start of the main clinical trial	3 (30.0%)
	After the top-line results are published	3 (30.0%)
	Considered from the planning stage of the main clinical trial	1 (10.0%)
	Other	1 (10.0%)
(3) When was EACT considered	Before the start of the pivotal clinical trial	0 (0.0%)
	At the end of subject inclusion of the pivotal clinical trial	3 (25.0%)
	After the start of the pivotal clinical trial	5 (41.7%)
	After the top-line results are published	4 (33.3%)

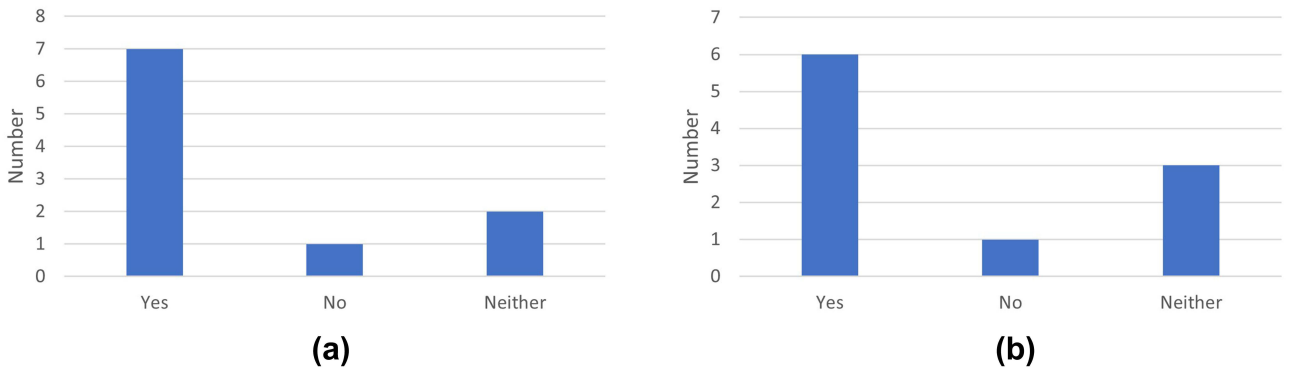

Figure 1 Survey results on single patient access system of compassionate use. (**a**) Survey results: Do you think there should be an expanded access system for individual patients in Japan? (**b**) Survey results: If there was a system for individual patients, would you want to do it?.

to be collected (six companies, 60.0%), simplification of procedures (six companies, 60.0%), and shortening the time to start EACT (five companies, 50.0%). Other opinions included: "The clinical trial framework is limited in terms of cost and resources". One respondent stated,

> Since it is burdensome to go to the trouble of writing a protocol just for an EACT, it would be good if there were a mechanism to put only the arm of the EACTs on the existing one (the one for the PCT),

and the main areas for improvement were cost and resources.

Discussion

CU is an system that allows investigational new drugs at the clinical trial stage to be used on patients with fatal diseases in the absence of alternative treatments. A CU mechanism system exists to provide earlier patient access to investigational new drugs when the benefit is deemed to outweigh the risk—given the entire risk of early access to investigational new drugs under investigation.

The EACT in Japan was conducted as a cohort type of trial and was not a CU for a single patient in each case. In addition, EACT in Japan was legally positioned according to the mechanism of clinical trials. Therefore, protocols, clinical trial notifications to the PMDA, and deliberations by the IRB take time. Furthermore, patients are required not to be affected by PCT inclusion in Japan, and EACT should only be initiated after completion of the PCT inclusion at the earliest.[14]

CU has long been practiced in the EU and has a robust operational framework.[18] The prototype of CU in the US began with the development of therapeutics against the Human Immunodeficiency Virus (HIV)/Acquired Immunodeficiency Syndrome (AIDS).[19] The current standard of application of the CU mechanism in Europe and the United States, as in Japan, is for patients whose lives are in danger because existing treatment methods cannot treat them. There are now cohort-type compassionate uses in Europe and the United States, but it can also be conducted on a single-patient basis in each case.[20,21] It is also a separate

Table 4 Improvements of the Expanded Access Clinical Trial

Points of improvements of the expanded access clinical trial	Financial assistance	8 (80.0%)
	Reduction in the scope of data to be collected	6 (60.0%)
	Simplification of the procedure	6 (60.0%)
	Shortening of the time to start expanded access clinical trials	5 (50.0%)
	Other	4 (40.0%)
	None	0 (0.0%)

licensing system from clinical trials. For example, single-patient INDs in the US may be approved for implementation as soon as a few days after the notification.[14]

Until now, we have examined EACT in Japan based on public information.[14] We found that CU in Japan began in 2016, with 36 trials having been conducted as clinical trials up to 2022. More than half of EACTs in Japan were initiated after the Approval Application, and most EACTs were implemented for a short period of less than one year before approval.[14]

Based on the results of this interview study, the reason for performing EACT was "due to it being requested by physicians and medical institutions", and requests from medical institutions were a significant factor in implementing EACT. The most common timing to consider EACT was "after the start of PCT" (41.7%). Moreover, many expressed a desire to save resources, effort, and time to improve EACT. This suggested that pharmaceutical companies may not have the resources to perform EACT. Regarding whether Single Patient IND should be performed, seven out of ten respondents said it should be performed, suggesting that there is room for consideration regarding the implementation of Single Patient IND. Based on the above points, we propose a revision of the EACT system in Japan. To the authors' knowledge, no study has interviewed pharmaceutical companies to clarify the current status of EACTs in Japan. Clarification of possible challenges to EACTs in Japan, as derived from these results, may provide an opportunity to revise the system and resolve these issues.

Drug lag once existed in Japan,[22] and drug loss is still a problem.[23] Recently, several attempts have been made to improve early patient access through various designation schemes and incentives to shorten development and review periods. For example, there are mechanisms for shortening development time, such as the SAKIGAKE designation system[24] and conditional approval system,[25] and for obtaining approval for additional indications without conducting clinical trials, such as the Public Knowledge-based Application.[26] However, many of these methods are based on overseas data or approval. Most importantly, the drug must be approved before patients can access it. In Japan, very few facilities participated in international collaborative trials of CU for the treatment of COVID-19 during the COVID-19 pandemic.[27–30] CUs are expected to be used in emergencies such as pandemics. For this purpose, we believe that a flexible operation of EACT—such as its use in single patients and a system that can be applied at an early stage—is necessary. The authors hope that patients will be able to access the drugs they have been waiting for as soon as possible after carefully examining the balance of risks and benefits of unapproved drugs.

Conclusion

An interview survey of ten pharmaceutical companies developing new drugs in Japan regarding expanded access clinical trials indicated that there were issues with the system. Many wished to improve the system by establishing a single patient access system, supporting resources, and simplifying procedures. Based on our interviews with 10 Japanese pharmaceutical companies, it was found that the system needed to be improved by introducing a single patient access system, providing supporting resources, and simplifying procedures. In Japan, about eight years have passed since EACT was established, and it appears a revision of the EACT legislation is due.

Abbreviations

CU, compassionate use; J-CU program, Japanese compassionate use program; EACT, Expanded Access Clinical Trials; PCT, pivotal clinical trial.

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