

January 22, 2016

To: Prefectural Health Department (Bureau)

From: Evaluation and Licensing Division,
Pharmaceutical Safety and Environmental Health Bureau,
Ministry of Health, Labour and Welfare
(Official seal omitted)

Clinical Trials Conducted on Ethical Grounds
-Japanese Compassionate Use System-

In order to resolve issue of pharmaceuticals and indications that are not yet approved in Japan but are approved in other regions such as in Europe and the United States (hereinafter, “unapproved drugs”), efforts have been made through development requests and public offerings on the basis of discussions by the “Expert Committee for Usage of Unapproved Drugs” and “Expert Committee on Unapproved and Off-label Drugs of High Medical Need” (hereinafter, the “Expert Committee for Unapproved Drugs”), and the period of regulatory reviews was shortened through enhancing review operations, by measures such as increasing the number of reviewers at the Pharmaceuticals and Medical Devices Agency (PMDA).

Although as a result the so-called drug lag (review lag) caused by the time period required for regulatory reviews appears to have been largely resolved, it is still likely that there are patients for whom the process from review to approval is too long, such as cases of life-threatening diseases that have no existing effective method of treatment.

On the basis of the final proposal (April 28, 2010) compiled by the “Committee for Investigation of Drug-induced Hepatitis Cases and Appropriate Regulatory Administration to Prevent Similar Sufferings,” the “Health Science Council Working Group on Revision of the Drug System” has discussed matters regarding access to unapproved drugs with high medical needs and prepared a compilation (January 24, 2012), which states, “Among unapproved drugs/medical devices with high medical needs for fatal diseases or diseases that greatly impede daily life with no method of treatment other than use of these drugs/medical devices, those limited to drugs/medical devices for which clinical trials are conducted in Japan are being considered with respect to a system allowing access, under certain conditions, for those patients who are not able to participate in clinical trials because they did not meet the study inclusion criteria. Although the Working Group is considering whether such a system should be

* This English version of the Japanese Notification is provided for reference purposes only. In the event of any inconsistency between the Japanese original and the English translation, the former shall prevail.

established, there were many opinions that such as system will require careful discussion prior to actual introduction.”

Moreover, this compilation states that this system should be applied “on the premise that the system does not impede activities to obtain product approval” and that in introducing this system, “the discussion should be undertaken keeping in mind a system that maintains a good balance where the drug subject to the system is provided by the pharmaceutical company conducting the clinical trial, without the development of that drug being impeded” upon ensuring “sufficient safety measures, such as of establishing a system for the collection of adverse reaction reports and to provide safety information to medical institutions”; i.e., the importance of maintaining a good balance between ensuring safety and smooth execution of clinical trials for marketing application is apparent.

In light of the above, it is stated in the “‘Japan Revitalization Strategy’ revised in 2014” (Cabinet approval on June 24, 2014) that “while development/approval of unapproved drugs/off-label drugs with high medical needs is advancing, discussion to introduce a system that enhances access to clinical trials for those patients who do not meet the inclusion criteria of such trials (i.e., a Japanese version of the USFDA’s “compassionate use” program), in order for the program to be implemented from the next fiscal year.” The Ministry of Health, Labour and Welfare (MHLW) asks that you inform relevant vendors and manufacturers under your supervision regarding the below details of this program planned for implementation from January 25, 2016.

MHLW also asks that you be advised of the “Enforcement of the Ministerial Ordinance to Partially Revise the Ministerial Ordinance on Good Clinical Practice for Drugs” (hereinafter, the “GCP Ministerial Ordinance”) (PSEHB Notification No. 0122-2 of the Pharmaceutical Safety and Environmental Health Bureau, MHLW, dated January 22, 2016).

1. Purpose of the System

Programs such as the “Expanded Access Program” and the “compassionate use” system, have been established in the United States and Europe on ethical grounds to provide unapproved drugs for the treatment of fatal diseases with no alternative therapeutic agents.

From the perspective of ensuring quality, efficacy and safety, drugs used in clinical practice are, in principle, those that have obtained marketing approval on the basis of the “The Act on Securing the Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical devices” (Act No. 145 of 1960; hereinafter, the “PMD Act”). However, it is assumed that for patients with fatal diseases, unapproved drugs are their last hope. There are demands to ensure access to unapproved drugs for these patients, provided that clinical use of those unapproved drugs does not impede their development, while at the same time, the balance between the risk due to the use of these unapproved drugs and the expected therapeutic benefit is maintained in the treatment of diseases that have a serious effect on the patients’ life and that have no existing effective method of treatment.

Therefore, introduction of a system similar to those already in place in Europe and the United

States has been discussed in Japan, and because careful consideration and establishment of the system were thought to be necessary so that no health damage is caused due to serious adverse reactions and so no impediment in the progress of the clinical trial prolongs in vain the unapproved state of the drug, discussions have been made in connection with the “Project to Enhance Access to Unapproved Drugs/Off-label Drugs with High Unmet Medical Needs” from 2013, with consideration of the state of system implementations overseas and their ways of approach.

Recently, a decision has been made to organize “clinical trials conducted on ethical grounds” (hereinafter, “expanded trials”) upon hearing opinions of relevant persons on how unapproved drugs should be provided on ethical grounds to patients who do not meet the inclusion criteria of clinical trials, with consideration of the possibility of implementing this system. Because this system will be implemented within the realm of the current clinical trial system in terms of laws and ordinances, it will be handled, in principle, in the same manner as existing trials, excluding the point that the government will be requesting sponsors or sponsor-investigators to consider conducting expanded trials on the basis of demands from patients’ primary physicians, as well as the point that the patient may be asked to partially pay the expense.

Note that the GCP Ministerial Ordinance was also revised to aim at reduction of the burden of sponsors or sponsor-investigators from the perspective of increasing the possibility of conducting expanded trials.

2. Summary of the system

(1) Scope of the system

- Because unapproved drugs are in the midst of their development, they may ultimately not gain approval. Particularly in the early stage of development when the scope of their indications or dosage/administration have not yet been defined, approval of a system to access such unapproved drugs should be carefully considered from the perspective of ensuring benefits that the patients may obtain even if those patients are in a condition where there is no other effective therapeutic agent. Therefore, this system focuses on investigational products that have gone through or are currently going through (after enrollment) a clinical trial that is in the final stage of development (generally clinical trials conducted to verify efficacy and safety after indications and dosage and administration have been established through a series of studies (hereinafter, “main trials”)) in Japan, when administration of the unapproved drug is thought to demonstrate a relatively high probability of its expected patient benefit.
- Because any undesirable effect of an expanded trial on smooth execution of the main trial may greatly delay the drug development, the expanded trial shall be conducted persistently on the premise that it does not affect the main trial.
- From the perspective of the balance between the risk of the use of unapproved drugs and the benefit of their expected efficacy, investigational products subject to this

system shall, in principle, be those for diseases that seriously affect the life of patients who cannot await drug marketing application, approval, or insurance coverage and that have no existing effective method of treatment.

(2) Positioning of clinical study

- From the perspective of ensuring safety in administration of unapproved drugs in Japan, the system shall be implemented within the realm of clinical trials under the GCP Ministerial Ordinance (after obtaining approval, including cases where the clinical trial will be continued as a post-marketing clinical study specified in Article 2, Paragraph 4 of the “Ministerial Ordinance on Good Post-marketing Study Practice” [MHLW Ministerial Ordinance No. 171 of 2004]).
- A protocol of the expanded trial is required to be submitted in advance. On the upper right corner of the front cover of the protocol, write “Expanded” (circle the word) in red, and in the remarks column, fill in “expanded trial” along with the receipt number of the clinical trial notification of the main trial. Note that in association with this system, the protocol notification of the main trial shall have “Main” (circle the word) written in red on the upper right corner of the front cover, and “main trial” filled in in the remarks column.

(3) Requests for an expanded trial and decisions to conduct the trial

- Because expanded trials are clinical trials conducted on ethical grounds, sponsors or sponsor-investigators shall not be impeded from conducting the trials voluntarily.
- Requests for expanded trials are not legally-binding; their execution is decided by the party who provides the investigational product. However, if the expanded trial is a investigator-initiated trial, the sponsor-investigator of the expanded trial shall make the decision based on their possibility of obtaining the investigational product.
- From the perspective of ensuring safety, experience and insight of the primary physician, who thoroughly understands the condition of the patient, are required in determining whether or not to conduct the expanded trial. Therefore, the primary physician shall be the one who will request the sponsor or sponsor-investigator to conduct the expanded trial.
- On ethical grounds, although it is desirable to respond to requests of primary physicians and patients as much as possible, there may be cases where expanded trials cannot be conducted due to the below reasons. In such cases, the sponsor or sponsor-investigator shall clearly explain, using Form 1, to the primary physician the reason the expanded trial cannot be conducted.
 - An effective method of treatment already exists, or the disease is not one that may seriously affect the patient’s life (reason of eligibility to the system).
 - No sufficient supply of the investigational product is available (absolute reason).

- There may be a negative influence on the main trial, such as when the main trial is during its enrolment period (reason of the period).
- Participation in the expanded trial is not recommended from the perspective of safety because the risk is clearly high in view of the patient's condition (individual reason).
- If the primary physician and patient who cannot participate in the main trial received a response from the sponsor or sponsor-investigator that an expanded trial cannot be conducted due to a "eligibility reason" (including cases where there are multiple reasons including "eligibility reasons") and do not agree with the "eligibility reason", the primary physician can contact the Evaluation and Licensing Division, Pharmaceutical Safety and Environmental Health Bureau of the Ministry of Health, Labour and Welfare (hereinafter, the "Evaluation and Licensing Division") and submit a request for consideration using Form 2 to explain the reason the patient cannot participate in the main trial and the necessity of an expanded trial, along with Form 1 of the response sent from the sponsor or sponsor-investigator.

Upon receiving the request for consideration, MHLW shall evaluate at the Expert Committee for Unapproved Drugs only the eligibility to the criteria of the system in terms of validity of conducting the expanded trial.

If the Expert Committee for Unapproved Drugs determined that the patient meets the eligibility criteria, MHLW shall request the sponsor or sponsor-investigator (in the cases of so-called investigator-initiated trial, the sponsor-investigator of the trial and the supplier of the investigational product used in the trial) of the main trial to consider conducting the expanded trial.

The sponsor or sponsor-investigator that received the request shall consider conducting the expanded trial once more and reply to the primary physician. Note that the conclusion of the Expert Committee for Unapproved Drugs is to be disclosed and can be viewed on the website of MHLW.

- The decision of conducting the expanded trial is made by the company, similarly to the system in Europe and the United States. However, be aware that there may be cases where the trial cannot be conducted if there is not enough supply of the investigational product; if there may be any influence on the main trial, such as when the main trial is during its enrolment period; or if participation in the expanded trial is not recommended from the perspective of safety in view of the condition of the patient.

(4) Protocol

- The protocol of the expanded trial shall be prepared on the basis of the protocol of the main trial, and its keynote shall be focused on safety verification which has been modified from the protocol of the main trial. Note that laboratory parameters

pertaining to indicators for verifying efficacy may be simplified or abbreviated to the extent that the safety of the patient is ensured.

- The PMDA clinical trial consultation offering may be used as necessary when preparing an expanded trial protocol.
- In principle, execution of an expanded trial is considered only after receipt of its request. However, as an exception, if a high social demand for conducting an expanded trial of the drug of the main trial is expected, it is desirable to consider conducting an expanded trial or preparing its protocol from the stage of preparing the protocol of its main trial.

For the present, expanded trials for the below drugs are assumed to be in high demand by the public.

- Drugs that are being studied in intermediate-size investigational new drug (IND) (protocol) or Treatment IND (protocol) under the Expanded Access Program (EAP) conducted in the United States (including those currently planned).
- Drugs that have applied for the SAKIGAKE designation system (limited to the indications or dosage forms that have applied for designation).
- Drugs designated as orphan drugs (limited to the designated indications or dosage forms).
- Drugs that were regarded as having high medical needs and requested for development in the Expert Committee for Unapproved Drugs (limited to the requested indications or dosage forms).

(5) Patients

- For those patients who hope to participate in an expanded trial, the expanded trial is critical for determining whether they have the opportunity for treatment. From the perspective of ensuring safety, however, whether or not patients who do not meet the inclusion criteria of the main trial can be included in the expanded trial must be carefully considered in terms of complications, stage of disease, and seriousness. Therefore, patients subject to the expanded trial shall be those who are medically/pharmacologically acceptable even if the inclusion criteria in the protocol of a completed or ongoing main trial are loosened.
- In the cases where a patient is not able to participate in an expanded trial determining from the protocol that has already been prepared prior to receiving the request for the expanded trial, the reason for this exclusion shall be explained to the patient's primary physician on the basis of the grounds that were considered when the protocol was prepared.

The protocol shall be reconsidered at the point when determined to be feasible.

(6) Trial site

- From the perspective of ensuring safety of subjects, because drugs subject to expanded trials are unapproved drugs, expanded trials shall be conducted by the principal investigator or subinvestigators of the main trial at medical institutions that have experience in administering the drug, that are assumed to have sufficient knowledge and experience of adverse reactions due to the drug, and that have gone through or is currently going through the main trial.

(7) Trial-associated financial burden

- In principle, the sponsor or sponsor-investigator bears the expenses of clinical trials. In expanded trials, however, a reasonable amount of the expenses for manufacturing, delivering, managing, and storing investigational products as well as expenses for the drugs of the same class (for drugs not covered by national health insurance) can be requested to the patient who will participate in the expanded trial.

Note that in view of the fact that expanded trials are conducted on ethical grounds unlike usual clinical trials, reimbursements that are usually paid in clinical trials are not necessarily required.

- The following requirements must be met in order to request patients to bear the expense.
 - Patient consent must be obtained upon providing a thorough explanation and written information so that the patient can clearly understand in advance the estimated patient payment and principles of the cost estimation.
 - Payment of the investigational product and drugs of the same class that are listed in the “National Health Insurance Drug Price List (NHI price table)” (MHLW Ministerial Announcement No. 60 of 2008) shall not exceed the pharmaceutical price.
 - The amount and principles of the estimation of the cost of any patient payment of investigational products and drugs of the same class must be reported to the Evaluation and Licensing Division.

(8) Study duration

- Because this system is implemented within the scope of policies related to clinical trials, expanded trials shall be concluded, in principle, at the point when the drug has received approval or disapproval, when the application has been withdrawn such as when the drug was found to demonstrate no efficacy, or when the drug development has been discontinued.

However, if administration of the investigational product must be continued after obtaining approval until initiation of marketing, the following measures shall be taken depending on by whom the clinical trial is initiated.

- Trials conducted by companies: Indicate in the protocol notification and protocol in advance so that the trial is automatically switched to a post-marketing clinical study after approval has been obtained.
- Investigator-initiated trials: Indicate in the protocol notification and protocol in advance so that the trial is automatically switched to a clinical study after approval has been obtained. Consult the Evaluation and Licensing Division in advance if continuation of the clinical trial is inevitable.

(9) Compensation

- Because expanded trials are conducted within the realm of clinical trials, appropriate measures for compensation shall be taken based on Article 14 or Article 15-9 of the GCP Ministerial Ordinance.

3. Handling of application data after application

- Patients in expanded trials are generally assumed to have higher risk than patients included in the main trial. From the perspective of evaluating safety, the details of this information shall be tabulated and reported at least once during product review after application in accordance with instructions from the PMDA review office. Because expanded trials are conducted on ethical grounds unlike usual clinical trials, the PMDA review office shall give consideration so that no excess burden is imposed on the applicant due to frequent tabulations.
- Because it is assumed that expanded trials will also be conducted during the application review process, data generated by these studies will generally not be included in the clinical data package at the time of application submission. There may be cases where necessary information may be added to package inserts if an expanded trial uncovers safety information pertaining to patients that can be anticipated to use the product after marketing.

4. Disclosure of trial information

(1) Disclosure of information on main trial

- Of the information that has been submitted to PMDA in the protocol notification, the following information on the main trial and expanded trial will be disclosed on the PMDA website.
 - Information on the investigational product (investigational ingredient code)
 - Name and contact information of submitter of trial notification (contact information will be prepared in a separate list)
 - Subject diseases
 - Trial phase (e.g., phase III)
 - Scheduled period of clinical trial

- Information presented in protocol notifications of main trials and expanded trials that are submitted to PMDA as from January 25, 2016 will be disclosed on the PMDA website by the end of the next month after submission. Disclosed data (excluding contact information) are those presented in the trial notification that was initially submitted.
- (2) Transition of a completed or ongoing main trial
- Data and the trial notification receipt number corresponding to items in above section (1) shall be compiled according to each trial and submitted to PMDA by February 29, 2016 for those main trials for which a protocol notification has already been submitted and for which their intended approval is expected. Such files must be in .xls or .xlsx format.
 - Information on the main trial submitted in accordance with the above will be added to the information on the main trial submitted as from January 25, 2016 on the PMDA website by March 31, 2016.

5. Miscellaneous, operational considerations of expanded trials

- (1) Request to medical institutions for cooperation in expanded trials
- While administration of unapproved drugs to patients in expanded trials conducted within the scope of clinical trials also requires the efficient and effective implementation of safety measures, conducting an expanded trial places a substantial burden on companies. Therefore, in light of the intent of this system, medical institutions, Contract Research Organizations (CROs), Site Management Organizations (SMOs), and other related institutions are requested to cooperate in distinguishing expanded trial contracts from those of routine clinical trials and to keep the total contract cost as low as possible, to minimize the burden on sponsors or sponsor-investigators.
- (2) Management of GCP-related matters in expanded trials
- For the implementation of expanded trials, the GCP Ministerial Ordinance has been revised as follows.
- For details, see related notifications that will be separately issued later on.
- [1] Clinical trials conducted on ethical grounds were defined as “expanded trials.” (Article 2, Paragraph 25 of the GCP Ministerial Ordinance)
- [2] In requests of expanded trials of investigational products used overseas or approved pharmaceuticals that are already marketed (including those stocked at medical institutions), the only information required to be indicated is the fact that the trial is “for clinical trial” (indicated in Japanese) and information on “name and address of the sponsor (if the sponsor is not located in Japan, indicate its name and the sponsor’s country of residence, as well as the name and address of the clinical trial in-country

representative)” (indicated in Japanese). (Article 16, Paragraph 1 of the GCP Ministerial Ordinance)

- [3] In requests of expanded trials, it is no longer prohibited to indicate the intended brand name, indications, and dosage and administration of investigational products. (Article 16, Paragraph 2 of the GCP Ministerial Ordinance)
- [4] In requests of expanded trials, it has been approved to divert stocks of medical institutions into use in clinical trials by adding labels on them for storage at an appropriate place at medical institutions, instead of having the sponsor directly deliver them, on the premise that those drugs that will be diverted to clinical trials are managed distinguished from other drugs. (Article 17 of the GCP Ministerial Ordinance).
- [5] If a sponsor-investigator is to conduct an expanded trial using an investigational product used overseas or an approved pharmaceutical that is already marketed (including those stocked at medical institutions), the only information required to be indicated is the fact that the trial is “for clinical trial” (indicated in Japanese) and “name, title, and address of the sponsor-investigator” (indicated in Japanese). (Article 26-2, Paragraph 1 of the GCP Ministerial Ordinance)
- [6] If a sponsor-investigator is to conduct an expanded trial, it is no longer prohibited to indicate the intended brand name, indications, and dosage and administration of investigational products. (Article 26-2, Paragraph 2 of the GCP Ministerial Ordinance)
- [7] If a sponsor-investigator is to conduct an expanded trial, it has been approved to divert stocks of medical institutions into use in clinical trials by adding labels on them for storage at an appropriate place at medical institutions, instead of having to obtain investigational drugs or having to receive the investigational drugs from the supplier, on the premise that those drugs diverted to clinical trials are managed distinguished from other drugs. (Article 26-3 of the GCP Ministerial Ordinance)
- [8] Because there are cases where subjects are asked to bear trial-related costs, “information concerning subject cost burden” was added as one of the items that are to be indicated in the written information handed to subjects when the investigator explains the details of the trial. (Article 51 of the GCP Ministerial Ordinance)

(Form 1)

Company's Determination regarding Participation in Clinical Trials Conducted on Ethical Grounds

To: (Name of primary physician)

MM/DD/YYYY

Control number	Indicate a code chosen by the submitter: "date of submission indicated on the upper right margin (YYYY/MM/DD (8 digits)) + 4 random letters" e.g., 20151225MHLW, 20151225phar, 20151225AbCd
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1. Information on product requested for expanded trial
(1) Name of marketing authorization holder:
(2) Investigational ingredient code:
(3) Name of drug (generic name or brand name): [if decided]
(4) Name of the indications under development (main trial):
2. Reason the expanded trial cannot be conducted
(1) Relevance to each reason (put a check on all relevant items)
<input type="checkbox"/> Reason of relevancy to the system (An effective method of treatment already exists, or the disease is not one that may seriously affect the patient's life.)
<input type="checkbox"/> Absolute reason (No sufficient supply of the investigational product is available.)
<input type="checkbox"/> Reason of the period (There may be a negative influence on the main trial, such as when the main trial is during its enrolment period.)
<input type="checkbox"/> Individual reason (Participation in the expanded trial is not recommended from the perspective of safety because the risk is clearly high in view of the patient's condition.)
<input type="checkbox"/> Miscellaneous
(2) Reason (Clearly explain each of the reasons)

Contact information	<u>Name:</u> _____
	<u>Name of affiliated organization:</u> _____
	<u>Address:</u> 〒 _____
	<u>Tel:</u> _____ <u>E-mail:</u> _____

(Form 2)

Request for Consideration regarding Participation in Clinical Trials Conducted on Ethical Grounds

To: Evaluation and Licensing Division,
Pharmaceutical Safety and Environmental Health Bureau,
Ministry of Health, Labour and Welfare

MM/DD/YYYY

Control number (fill in the number indicated on the document on company's determination)
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1. Information on the product for which an expanded trial is requested (fill in information regarding the content indicated on the document on company's determination)	
(1) Name of marketing authorization holder:	
(2) Investigational ingredient code:	
(3) Name of drug (generic name or brand name): [if decided]	
(4) Name of the indications under development (main trial):	
2. Reason for considering that other existing therapeutic agents/treatments are unsatisfactory	
(1) Disease name:	
(2) Reason the current therapy or treatment with the approved drug is unsatisfactory	
	1) Name of current treatment or approved therapeutic agent:
	2) Reason the efficacy of the therapy is unsatisfactory or not applicable:
(3) Reason the patient cannot participate in the main trial:	
(4) Scientific evidence for considering that a clinical trial conducted on ethical grounds is necessary (Explain the reason the patient cannot wait for normal drug assessment/regulatory review, or the reason for considering that the benefit of therapy with the investigational product outweighs the risk.)	

Contact information of physician <u>Name:</u> _____
<u>Name of affiliated organization:</u> _____
<u>Address:</u> 〒 _____
<u>Tel:</u> _____ <u>E-mail:</u> _____

N.B. Submit to MHLW along with the response from the sponsor or sponsor-investigator (Form 1).