

**Points to Be Considered by the Review Staff  
Involved in the Evaluation Process of New Drug  
(FINAL)\***

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Pharmaceuticals & Medical Devices Agency

**1. Purpose**

The purpose of this document is to promote an understanding among the review staff involved in the evaluation of new drugs, of the basic principles and major points that need to be considered in being involved in the drug evaluation process at the Pharmaceuticals and Medical Devices Agency (PMDA).

**2. Scope**

This document summarizes the points that need to be considered during the actual evaluation process of drugs after a new drug application has been submitted, covering all new drugs which are reviewed by teams at the PMDA.

However, the points covered in this document are limited to basic points generally considered, and it should be kept in mind that there may be many other points that need to be judged on a case-by-case basis.

Especially, for drugs in the field of orphan diseases or serious diseases for which existing therapies have not yet been established, final decisions should not be based exclusively on the points covered in this document, but should also take into consideration other points such as clinical significance of the drug. Even for such drugs, however, the scientific evaluation using appropriate data should be based on a full understanding of the purpose and principle of this document.

In addition, although the results of quality and non-clinical studies are also evaluated in the new drug evaluation process, this document mainly describes points related to clinical studies that have arisen as major issues of discussion in the past.

**3. Basic Principles Related to the Evaluation Process of New Drugs**

Because the principal mission of the PMDA is to rapidly provide safe and effective drugs to patients, the PMDA reviewers involved in the evaluation processes of new drugs should basically perform his/her duties bearing the following in mind.

- Attempts should always be made to acquire scientific knowledge and grasp the domestic and international trends linked to the drug evaluation.
- Evaluation should be primarily based on the latest scientific findings, but the time and background of the conducted study and previous decisions for similar drugs should also be taken into consideration.
- Judgment of approval/non-approval should be based on scientific and objective evaluation of the data provided, taking into account the objective evaluation of benefits/risks, with an understanding also from the patient's standpoint.
- For any concerns that might arise during the new drug evaluation process, opinions should be presented proactively, regardless of his or her position or responsibilities, in order to determine the best solution on behalf of the PMDA.
- For any concerns that might arise during the new drug evaluation process, attempts should be made to find the appropriate solution by offering advice to the applicant while also gaining understanding from various related quarters after explaining the reason and grounds for that particular concern, and by obtaining cooperation from related PMDA divisions and Ministry of Health, Labour and Welfare (MHLW) and other related organizations.
- In order to facilitate smooth evaluation, attempts should be made to promote mutual understanding with the applicant, always keeping in mind the need to maintain good communication at all times for securing a fair and neutral standpoint.
- To ensure provision of objective and accurate information to the patients and healthcare professionals, guidance should be provided to the applicant while closely collaborating with related PMDA divisions and the MHLW and other organizations.

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\* This translation of the original Japanese text that was published on April 17th, 2008 is provided for reference purpose only. In case of inconsistency, the Japanese text shall prevail.

- To ensure transparency, the review report should be prepared such that even a third person with a certain level of knowledge can easily understand the scientific facts and problems identified in the new drug evaluation process.

#### 4. Points to Consider During the New Drug Evaluation Process

New drug evaluation processes based on the Pharmaceutical Affairs Law should be undertaken after confirming that the new drug applied for does not fall under the “condition of approval rejection” prescribed by law.

In case it is identified as falling under the condition of approval rejection, or falling under this condition after approval for any reason, the approval should be withdrawn or change of the approved contents should be requested.

When conducting evaluation of a new drug at the PMDA, judgment for approval or non-approval should also be based on the regulations of the Pharmaceutical Affairs Law, and the following 5 points should mainly be considered.

- ① Has the reliability of the conducted studies and submitted documents been ensured?
- ② Is the efficacy in the study population considered to be more effective than placebo according to the results of properly designed clinical studies?
- ③ Do the obtained results have clinical significance?
- ④ Are there any unacceptable risks as compared to the benefits?
- ⑤ Can the drug be supplied continuously with stable efficacy and safety from a quality assurance standpoint?

Meanwhile, a drug cannot be approved when the clinical significance is unclear because efficacy has not been shown in the study population of clinical studies, or when an unacceptable risk is recognized in comparison with the benefits.

It should be noted that even in the case when the data provided justifies approval of a drug, this would not necessarily assure efficacy or acceptability of the recognized risk in comparison with the benefits in each individual patient included in the study population, because the new drug evaluation process is designed for evaluation of the efficacy and safety of a new drug in the study population, as a whole, of the clinical study. That is, the viewpoint would naturally be different for the evaluation process of a drug for patients as a population and for actual individual patients in medical practice.

Especially in clinical studies conducted prior to approval, since the number of patients for evaluation are limited and various restrictions are posed by the patient inclusion/exclusion criteria, prohibited concomitant medications and other criteria, careful monitoring of the efficacy and safety of a drug should be continued even after approval.

Therefore, in order to ensure that the manufactured and marketed drugs are properly selected and administered by patients and healthcare professionals such as medical doctors, the PMDA review division should provide guidance to the applicant while closely collaborating with related PMDA divisions, the MHLW, and other related organizations, and always keep in mind that objective and fair information related to the benefits/risks of a drug should be clearly and fully communicated to patients and healthcare professionals.

Particular attention should be paid in the case of new drugs with serious risks, to ensure appropriate communication of the facts known regarding the risks.

(1) For evaluating ① to ⑤, it is necessary to conduct a comprehensive evaluation taking into consideration the following points. However, because the points can differ according to the characteristics of a drug, the submitted study results, and other factors related to each new drug, it should be noted that the evaluation points are not always limited to the following.

- 1) Are the development strategy, data package and study designs appropriate in line with the intended indications and usage?
- 2) Has the data reliability in the submitted documents been ensured?
- 3) Are there no significant differences in the efficacy and safety caused by ethnic factors (when foreign clinical data are submitted as the pivotal confirmatory data)?
- 4) Has superiority been confirmed against placebo or other doses in the efficacy evaluation?
- 5) Is the range of the placebo responder rate presumed to be constant in the efficacy evaluation?
- 6) Has non-inferiority/superiority against an active control been confirmed in the efficacy evaluation?

- 7) Has the efficacy been confirmed sufficiently even in an unblinded study without a control?
- 8) Are there any discrepancies among the pivotal study results?
- 9) Can the recognized risks be controlled and are the risks acceptable when considering the benefits?
- 10) Are there any points of concern in regard to the non-clinical study results in the submitted application documents?
- 11) Have the appropriate processes and strategies been provided for assuring the quality of the product that would allow continuous manufacture of a drug which shows efficacy and safety equivalent to those suggested by the data in the submitted application document?

Supplementary notes for above points 1) to 11) and points to consider on the requisite clinical study results.

- In order to ensure the reliability of the results, it would be desirable, in principle, for the efficacy to have been confirmed in “two or more randomized controlled studies.” “Two or more randomized controlled studies” implies not only confirmatory studies, but also includes exploratory dose-finding studies with similar results to those of confirmatory studies, and overseas clinical studies whose results can be extrapolated based on the results of a domestic bridging study.
- When the superiority of a drug is confirmed over placebo, a non-inferiority study with existing drugs may not always be necessary. However, if the clinical significance of a drug is unclear, even in the case when a standard drug has already been established for the indicated disease and the superiority of drug against placebo has been confirmed, it may be appropriate to conduct a non-inferiority study in order to clarify the clinical positioning of a drug with respect to the standard drug (e.g., anti-infective drugs, etc.). Additionally, to clarify the positioning of a drug with respect to the existing drugs, a controlled study with 3 groups including placebo, the investigational drug, and an existing drug as the control drug, may be useful, even if statistical power is not secured.
- In a disease area where the placebo responder rate is presumed to be constant, results showing the investigational drug’s non-inferiority against an existing drug or results from an objective and appropriate clinical study even without a control group may be sufficient for the evaluation.

(2) For items indicated in (1), several points should be considered for making a judgment. The possible points that would need to be considered are listed below as an example. However, since the important points would depend on the profile of each new drug, all of the points listed below may not always be automatically applicable, while points not listed below may need to be considered.

- 1) For “Are the development strategy, data package and study designs appropriate in line with the intended indications and usage?”
  - Does the developed new drug meet the medical needs?
  - Have all the necessary study results been submitted?
  - Have the study subjects been appropriately defined and selected?
  - Are the determined administration and dosage appropriate?
  - Have the number of cases been determined appropriately?
  - Have randomization and blinding in the study been implemented appropriately?
  - Is the endpoint appropriate?
  - Have adverse events been appropriately collected and evaluated?
- 2) For “Has the data reliability in the submitted documents been ensured?”
  - Have the reliability of the quality, non-clinical and clinical data been ensured?
  - Have standards such as GLP, GCP, etc., been complied with?
- 3) For “Are there no significant differences in the efficacy and safety caused by ethnic factors (when foreign clinical data are submitted as the pivotal confirmatory data)?”
  - Have an adequate number of Japanese cases been included?
  - Have ethnic factors (intrinsic and extrinsic factors) described in the ICH E5 guideline been considered?
  - Is the pharmacokinetic profile in the Japanese population similar to that in foreign populations?

- Is the dose-response relationship in the Japanese population similar to that in foreign populations?
  - In the case where ethnic factors (intrinsic and extrinsic factors) are considered to be different, would the factors have any major impacts on the efficacy and safety?
  - Have any specific risks been recognized in the Japanese population?
- 4) For “Has superiority been confirmed against placebo or other doses in the efficacy evaluation?”
- Has the superiority been confirmed against placebo or other dosage groups in a placebo controlled study or in a clinical study with more than 2 dosage groups?
  - Is the endpoint appropriate and does the significant group difference determined have clinical significance?
  - Has the blinding been appropriately assured?
  - Does any confounding factor exist and would it have a major impact on the results?
- 5) For “Is the range of the placebo responder rate presumed to be constant in the efficacy evaluation?”
- Has it been confirmed that the placebo responder rate is constant from the results of placebo controlled studies conducted in the past?
  - Even if a placebo controlled study has not been conducted, is it possible to presume that the placebo responder rate for the indicated disease is virtually constant according to the disease characteristics, correlativity of pharmacokinetics, clinical effects, etc?
  - Is it possible to presume that the placebo responder rate for the indicated disease is virtually constant according to published reports, academic guidelines, etc?
- 6) For “Has non-inferiority/superiority against an active control been confirmed in the efficacy evaluation?”
- Is the control drug appropriate?
  - Is the dosage of the control drug appropriate?
  - Has the blinding been appropriately assured?
  - Is the endpoint appropriate and is the pre-determined non-inferiority limit ( $\Delta$ ) appropriate (in the case of a non-inferiority study)?
  - Is the endpoint appropriate and does the significant group difference determined for superiority have clinical significance (in the case of a superiority study)?
  - Does any confounding factor exist and would it have a major impact on the results?
- 7) For “Has the efficacy been confirmed sufficiently even in an unblinded study without a control?”
- Is there any rational reason for a placebo controlled study and non-inferiority study with existing drugs to not have been conducted?
  - Has efficacy been clearly confirmed in clinical studies of similar drugs?
  - Is the pharmacological mechanism clear?
  - Has the primary endpoint been objectively evaluated?
- 8) For “Are there any discrepancies among the pivotal study results?”
- Even though non-inferiority has been confirmed, has superiority to placebo been denied in other clinical studies?
  - Has the efficacy been confirmed in multiple studies?
  - Has the stability of the study results been assured from the disease characteristics, status of similar drugs, etc?
- 9) For “Can the recognized risks be controlled and are the risks acceptable when considering the benefits?”
- Has the efficacy been clearly confirmed?
  - Have factors related to the recognized risk been clearly identified?
  - Has any effective treatment been identified to prevent/inhibit occurrence of the recognized risk?
  - Is the recognized risk acceptable, even if it is serious, when considering the benefits?

- 10) For “Are there any points of concern in regard to the non-clinical study results in the submitted application documents?”
- Has appropriate and sufficient consideration been given while evaluating the efficacy and safety of the drug for human use?
  - Is there any important discrepancy in the results between the non-clinical and clinical studies (pharmacological mechanism, pharmacokinetic profile, etc.)?
  - Are there any results that may cause concern on evaluations of the safety of the new drug in humans, even though such results have not been recognized in clinical trials?
- 11) For “Have the appropriate processes and strategies been provided for assuring the quality of the product that would allow continuous manufacture of a drug which shows efficacy and safety equivalent to those suggested by the data in the submitted application document?”
- Has an appropriate quality index reflecting the efficacy/safety been provided as the approval item together with the appropriate experimental methods and standards?
  - Has the manufacturing process control which is important for quality assurance been provided as the approval item?
  - Can the new drug with stable efficacy and safety be manufactured continuously in compliance with GMP standards?

(Notes regarding the check sheet to summarize important points upon evaluation )

- The check sheet is prepared to clarify and share points for discussion and argument within the review team, and utilize these to organize the rationale for the judgment of approval/non-approval, but the points shown here may not always automatically lead to the conclusion.
- Put a ✓ against each column. However, since descriptions in each column are only for reference, a checkmark can be put at any position of each column, assuming that an upper position means higher level and a lower position means lower level.
- \*: A), B), C) are in random order and one can proceed to the next step if everything is confirmed
- \*\*: Besides medical countermeasures, sometimes it is appropriate to consider other measures, such as limiting the prescription only by medical specialists, registration of doctors/patients, restriction of drug delivery and limiting the usage to hospitalized patients, according to the risk and types/degree of the adverse events.

	A) Development concept /design*		B) Reliability assurance*	C) Efficacy*		D) Reproducibility of study results	E) Risk/Benefit**		F) Consideration of serious/rare diseases and social needs
	A-1) Data package	A-2) Study design		C-1) Usage of overseas data	C-2) Efficacy evaluation		E-1) Medical countermeasures for adverse events	E-2) Acceptability of risks in comparison with benefits	
To next step without any concerns	<ul style="list-style-type: none"> <li>• In general, required studies have been conducted.</li> <li>• In general, required studies have not been conducted, but the studies conducted are enough for a scientific review.</li> </ul>	<ul style="list-style-type: none"> <li>• Considering the study objectives each item in the protocol is appropriate.</li> <li>• Part of the protocol is inappropriate but it is not crucial, or, the review can be continued with some amendment.</li> </ul>	<ul style="list-style-type: none"> <li>• Data reliability is ensured.</li> <li>• Recognized violations are not crucial and the review can be continued with some amendments.</li> </ul>	<ul style="list-style-type: none"> <li>• Package consisted only in domestic studies.</li> <li>• Overseas study results for review are included.</li> <li>• Some overseas studies do not meet the standards for review, but sufficient data from the Japanese population is submitted.</li> </ul>	<ul style="list-style-type: none"> <li>• Superiority to placebo or other dosages has been confirmed.</li> <li>• For a disease area where the placebo responder rate is presumed constant, the non-inferiority against control drugs has been confirmed.</li> <li>• Efficacy has been sufficiently confirmed even in an unblinded, uncontrolled study.</li> </ul>	<ul style="list-style-type: none"> <li>• There are no discrepancies between the studies and reproducibility of the results have been ensured.</li> <li>• Discrepancy has been observed but not critical and it is possible to ensure the efficacy.</li> </ul>	<ul style="list-style-type: none"> <li>• Only non-serious adverse events have been observed.</li> <li>• Serious adverse events have been observed, but the frequency was low and medical counter-measures are available.</li> </ul>	<ul style="list-style-type: none"> <li>• Risks are low, and benefits are shown to outweigh the risks.</li> </ul>	<ul style="list-style-type: none"> <li>• Approved if all points within this range are fulfilled.</li> </ul>
To be judged in consideration of the severity of the disease, alternative therapy and other items	<ul style="list-style-type: none"> <li>• In general, required studies have not been conducted, and the studies conducted are not sufficient for scientific review, but considerations are possible.</li> </ul>	<ul style="list-style-type: none"> <li>• Part of the protocol is inappropriate, and insufficient for scientific review, but considerations are possible.</li> </ul>	<ul style="list-style-type: none"> <li>• Recognized violations are crucial and difficult to amend, but considerations are possible.</li> </ul>	<ul style="list-style-type: none"> <li>• Some overseas studies do not meet the standards for review and sufficient data from the Japanese population have not been submitted, but considerations are possible if both are taken into account.</li> </ul>	<ul style="list-style-type: none"> <li>• Efficacy has not been confirmed but suggestive study results have been submitted. Thus, considerations are possible if common scientific knowledge or overseas study results are taken into consideration.</li> <li>• Common scientific knowledge has not been established, but considerations are possible with suggestive study results.</li> </ul>	<ul style="list-style-type: none"> <li>• Discrepancies are noted and reproducibility of the results has not been ensured, but considerations are possible.</li> </ul>	<ul style="list-style-type: none"> <li>• Serious adverse event have been reported at a low frequency, but no medical counter-measures have been established.</li> <li>• Serious adverse event have been reported at a high frequency, but medical counter-measures are available.</li> </ul>	<ul style="list-style-type: none"> <li>• Risks are low and efficacy is suggestive but evidence is insufficient. Thus, considerations on benefits/risks are necessary.</li> <li>• Strong evidence of efficacy is available but the risks are crucial. Thus, considerations on benefits/risks are necessary.</li> </ul>	<ul style="list-style-type: none"> <li>• If either one point falls under this range, approval or non-approval should be judged considering with the seriousness of the disease, availability of alternative therapy, and other points.</li> </ul>
Withdrawal	<ul style="list-style-type: none"> <li>• In general, required studies have not been conducted, and no scientific investigations have been performed, thus review is impossible to continue.</li> </ul>	<ul style="list-style-type: none"> <li>• Part of the protocol is inappropriate and review is impossible even if other factors are taken into consideration.</li> </ul>	<ul style="list-style-type: none"> <li>• Review is impossible to continue due to crucial violations.</li> </ul>	<ul style="list-style-type: none"> <li>• Review is impossible to continue, because only overseas studies without meeting the standards for review have been submitted.</li> </ul>	<ul style="list-style-type: none"> <li>• Efficacy has been denied.</li> </ul>	<ul style="list-style-type: none"> <li>• Crucial discrepancies have been observed and it was concluded that efficacy was denied.</li> </ul>	<ul style="list-style-type: none"> <li>• Serious adverse events have been reported at a high frequency and no medical counter-measures have been established.</li> </ul>	<ul style="list-style-type: none"> <li>• Risks are crucial and benefits have not been shown to outweigh the risks.</li> </ul>	<ul style="list-style-type: none"> <li>• Withdrawal if any of the points fit within range.</li> </ul>