



Analysis of new drugs whose clinical development and regulatory approval were hampered during their introduction in Japan

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SUMMARY

What is known and Objective: Many drugs fail during development. However, detailed reasons for failure during drug development are almost never disclosed. We focused on the drugs whose clinical development and registration were initially hampered, but which were finally approved to identify reasons that delayed their marketing approval in Japan.

Methods: We analysed 727 new drug applications (NDAs) approved in Japan between 2001 and 2011.

Results and Discussion: Fifty-three NDAs had serious and identifiable problems during drug development. Of these, 43 NDAs had 'problem related to clinical data'. We found that the problems for withdrawal of these NDAs could be ascribed largely to inappropriate clinical data package and study design for supporting the intended indications and usage and to unclear clinical results for defining dosage regimen or efficacy of the drugs.

What is new and Conclusion: Our results indicate the importance of careful determination of the optimal dosage regimen and the choice of objective endpoints in clinical trials. Further, it is important to establish a clear strategy for generating the clinical data package, to include careful design of clinical trials on the basis of the nature of the target disease and target population. For drugs marketed in Japan, there is a need to include sufficient numbers of Japanese patients in the trials.

WHAT IS KNOWN AND OBJECTIVE

The rate of successful new drug development has been stagnant over recent years. Only a small portion of all drugs (current success rate, 4%; maximum possible success rate, 19%) that entered phase 1 trials between 1999 and 2004 were finally approved by the US Food and Drug Administration by June 2009.¹ The corresponding success rate in Japan between 2000 and 2008 was estimated to be 44%.² The probability of successful transition from phase 1 trial to entry in the market seemed to be higher in Japan than in other regions (i.e. the United States and the European Union). A delay in clinical development in Japan compared with that in the other countries may be a reason for this difference.^{3–7}

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The delay in clinical development in follow-on regions, including Japan, has several advantages in that it enables developers in the follow-on regions to use results of previous clinical trials in foreign countries and to take into account the foreign development process and decisions made by the different regulatory authorities.

The probability of successful transition from each clinical stage of drug development (i.e. phase 1, phase 2, phase 3 and submission) into the market increases as the drug progresses to the subsequent stages.⁸ However, a small proportion of submitted new drug applications (NDAs) still fail to be approved by the regulatory authorities.^{1,8,9} In Japan, 58 (9.0%) of the 643 NDAs filed between 2004 and 2010 were withdrawn.¹⁰

Information on the reasons for failure to gain approval may help improve the design of clinical trials and the clinical data package submitted in support of the application of future drugs and thereby improve their success rate and reduce the time required for their development. However, obtaining detailed information about these drugs is extremely difficult because the information about the causes of failure of drug development is almost never disclosed.

To date, several studies have focused on drug development failures and reported reasons such as lack of efficacy, safety concerns and commercial problems.^{9,11–13} However, to our knowledge, no studies have examined the detailed reasons why the efficacy of drugs was not shown in clinical trials or the details about the safety concerns.

In this study, we focused on the drugs that had initially failed clinical development but were subsequently approved, that is, we studied the drugs for which the approval application was withdrawn or some of the 'proposed indications and usage' or 'proposed dosage and administration' in the application were not initially approved by the Japanese regulators. Their subsequent approval required remedial action (e.g. undertaking an additional clinical trial). The information about these drugs is available on the official website of the Pharmaceuticals and Medical Devices Agency (PMDA).¹⁴

The purpose of this study was to analyse the information about these drugs in detail and to discuss critical issues to help optimize drug development.

METHODS

We investigated all NDAs (including supplemental NDA) approved in Japan between April 2001 and March 2011 on the basis of review papers and summary of registration documents, which could be accessed from the official website of PMDA. Of all

NDA, we identified some NDAs that were withdrawn or in which some of 'proposed indications and usage' or 'dosage and administration' were deleted because of the PMDA reviews, and subsequently, another application was filed after necessary actions were taken, and the application was finally approved. We examined the reasons for withdrawal of these NDAs and deletion of some indications in these NDAs.

RESULTS AND DISCUSSION

Of 727 NDAs approved in Japan between April 2001 and March 2011, 53 were rejected at least once in the review process, but were finally approved. The main reasons for withdrawal of an NDA or rejection of some 'proposed indications and usage' or 'proposed dosage and administration' in the NDA are shown in Table 1. The major reason of the 53 NDAs was 'problem related to clinical data' and accounted for 81% (43 NDAs).

Investigation of NDAs classified into 'problem related to clinical data'

We analysed the 43 NDAs with failures that were categorized as 'problem related to clinical data'. Of these 43 NDAs, the NDAs for clozapine and bepridil hydrochloride hydrate were withdrawn twice, and they were counted as two NDAs. The NDA for loratadine was also counted as two NDAs because a dose-finding trial and a confirmatory trial for each approved indication (i.e. allergic rhinitis and urticaria) of loratadine were simultaneously requested in one NDA review. We closely examined the 46 NDAs and classified them into five categories according to detailed reasons in the light of 'points to be considered by the review staff involved in the evaluation process of a new drug' in Japan.¹⁵ The five categories and the number of NDAs classified under each category are shown in Table 2.

The target diseases for the 46 NDAs classified under the category of 'problem related to clinical data' are shown in Table 3. No significant difference was observed in the numbers of NDAs by therapeutic area, but cancer and cardiovascular diseases were the most popular targets followed by infectious diseases, central

Table 1. Main reasons for withdrawal of new drug application (NDA) or rejection of 'proposed indications and usage' or 'proposed dosage and administration'

Main reason	Number of NDAs (%)
Problem related to clinical data	43 (81)
Change of application category	5 (9)
Problem related to CMC/non-clinical data	2 (4)
Unknown	3 (6)
Total	53 (100)

Change of application category: for example, an NDA for indication 'B' was filed under the category of 'new active ingredients' during the regulatory review of a previous NDA of the same drug for another indication 'A'. Thus, the application for indication 'B' has to be withdrawn and resubmitted under the category 'new indication' after the application for indication A was approved.

Unknown: review reports did not have sufficient descriptions, and we were unable to determine exact reasons.

CMC, chemistry, manufacturing and control; NDA, new drug application.

nervous system diseases, metabolic diseases and allergic diseases. The proportion of all the approved drugs for these target diseases from 2004 to 2010 was 14%, 7%, 13%, 6%, 17% and 2%, respectively.¹⁶

Twelve NDAs classified under category A and 16 NDAs classified under category B are further examined in the following section, the details of these NDAs are shown in Table S1.

Eleven NDAs classified under category C were withdrawn because of the violation of Good Clinical Practice (GCP) (7/11) and defective submitted documentation (4/11). Subsequently, additional clinical trials were conducted under GCP or the submitted documents were corrected.

Three NDAs were classified under category D. For botulinum toxin type A, it was necessary to examine the safety of this drug carefully because two cases of death were recognized in the clinical trial in patients with spasmodic torticollis. Subsequently, the clinical trial was performed to examine the minimal effective dose. For clozapine, the development was suspended due to the reports of agranulocytosis in patients with schizophrenia from overseas. Later, focus was placed on the efficacy of clozapine in patients with treatment-resistant schizophrenia, and the additional clinical trial in these patients was conducted. For temsirolimus, it was necessary to examine the result of phase 2 trial carefully because the incidence rate of interstitial pneumonia in Japanese patients tended to be high in the trial. Subsequently, another application was filed after the result of phase 2 trial was investigated minutely.

Four NDAs were classified under category E. For three of those NDAs (human-activated protein C, bepridil hydrochloride hydrate and repaglinide), the development was initiated again after the intended indication and usage were altered. For another product (ketoprofen), the PMDA judged that tapes without cooling effect should be used for treatment of chronic diseases rather than for acute diseases. But the development of ketoprofen tape for treatment of muscle pain was re-initiated as other drug tapes were approved and ketoprofen tape was being used off-label.

NDA profiles classified into category A (strategic and data package problems)

For the 12 NDAs classified as category A, we analysed the reasons why the NDAs were withdrawn or why some of the 'proposed indications and usage' or 'proposed dosage and administration' in the NDA were deleted. We categorized these reasons into two groups: category A1, 'The data package was inappropriate', and category A2, 'The clinical study design was inappropriate'. Most of the NDAs were categorized into the former group (Table 4).

The details of the NDAs classified under the category A1 were as follows. For five NDAs (oseltamivir phosphate [2004 and 2009 approved], rocuronium bromide, candesartan cilexetil/hydrochlorothiazide combination and somatropin [genetic recombinant drug]), it was necessary to perform a confirmatory trial in Japan because the bridging strategy was inappropriate or unsuccessful. For two NDAs (azithromycin hydrate and basiliximab [genetic recombinant drug]), the Japanese clinical trials for the target disease were not undertaken. For one product (biapenem), the sample size in the Japanese clinical trial was too small for the intended indications. For one product (clozapine), it was necessary to perform a clinical trial to confirm that the patient monitoring system for minimizing the risks in the event of agranulocytosis can be operated successfully in general hospitals and dedicated psychiatric hospitals. For another product (nogitecan hydrochloro-

Table 2. New drug applications classified as 'problem related to clinical data'

Category	Detailed reason	Number of NDAs (%)
A	The development strategy, data package and study designs were not in line with the intended indications and usage	12 (26)
B	The rationale for selecting the dosage regimen was unclear or the efficacy was not confirmed according to the results of the clinical trials	16 (35)
C	The reliability of the data in the submitted documents was not ensured	11 (24)
D	Incidence of serious adverse events	3 (7)
E	The clinical usefulness was unclear	4 (9)
Total		46 (100)

NDA, new drug application.

ride), the PMDA judged that an additional clinical trial was necessary to evaluate efficacy with a valid endpoint.

Most of the NDAs categorized under category A1 were withdrawn because of unsuccessful bridging strategy (5/10). Therefore, information of the cases of unsuccessful bridging strategy should continue to be collected, and the reasons for failure of the bridging strategies should be examined. These results suggest that when a bridging strategy is being planned, it is important to design an adequately planned and well-organized bridging study and to take account of the successful bridging strategy of drugs already approved.¹⁷ In addition, when a clinical data package is being created, it is important to consider the kind of clinical study design necessary and the number of patients required in line with the intended indications and usage.

Two NDAs were classified as category A2. For one product (maxacalcitol), it was necessary to perform a controlled trial that took account of the characteristics, number of patients and age predilection of the target disease. Only unblinded studies without a control were performed at the time of first submission. For another product (tegafur/gimeracil/oteracil potassium combination), the PMDA judged that the clinical study was inappropriate for evaluating the efficacy because the inclusion criteria were inappropriate.

These results suggest that while designing a clinical study, it is important to take account of the nature of the target disease, the number of patients and the development strategy of drugs already approved for a similar indication.

NDA profiles classified into category B (insufficient rationale)

Sixteen NDAs were classified as category B. These NDAs were grouped into one or two categories B1–B3 (Table 5) on the basis of: 'B1, deficiency in the evidence for an optimal dosage regimen' (12 NDAs); 'B2, deficiency in the evidence for the maximum dose' (two NDAs, vardenafil hydrochloride hydrate and irbesartan); and 'B3, efficacy not confirmed in a confirmatory trial' (seven NDAs). Of the seven NDAs classified into category B3, five NDAs were classified into category B1 and B3, and two NDAs (pronase and cetirizine hydrochloride) into only category B3. These results indicated that there often was difficulty in establishing appropriate evidence for the proposed dosage regimen.

Six NDAs were classified as category B1. For sumatriptan succinate and bepotastine besilate, the PMDA judged that the results of dose–response study in the phase 2 trial with multiple-dose regimens were unclear. Each applicant conducted an additional trial with multiple-dose regimens to examine the dose–response. For flecainide acetate and bepridil hydrochloride hydrate, the design of the dose-finding study with multiple-dose regimens was inappropriate (e.g. non-blinded, dose escalation design). For each drug, an additional trial with multiple-dose regimens was conducted using a double-blinded, parallel study design. For pirfenidone, the evidence supporting the efficacy was deficiency in the result of a phase 2 study with a single-dose regimen, and so, an additional trial with multiple-dose regimens was conducted. For tacrolimus hydrate, the validity of the methods used for dose adjustment in the phase 2 study with multiple-dose regimens was not sufficient. A phase 3 study was not conducted. So an additional trial with a single-dose regimen was conducted to confirm the suitability of the proposed novel method for dose adjustment. For febusostat, the PMDA concluded that further examination of the optimal dose and method of administration was necessary because of the occurrence of adverse events, and then an additional trial with multiple-dose regimens was conducted.

Five NDAs were subclassified as categories B1 and B3. For loratadine (indication for allergic rhinitis and urticaria), the result of a dose–response study in the phase 2 trial with multiple-dose regimens was unclear, and the design of a phase 3 study was

Table 3. Target diseases for the 46 NDAs identified under the category 'problem related to clinical data'

Target disease	Number of NDAs (%)					
	Category A–E	Category A	Category B	Category C	Category D	Category E
Cancer	7 (15)	2	0	4	0	1
Cardiovascular diseases	7 (15)	1	5	1	0	0
Infectious diseases	6 (13)	4	0	2	0	0
Central nervous system diseases	5 (11)	2	2	1	0	0
Metabolic diseases	4 (9)	0	3	0	0	1
Allergic diseases	4 (9)	0	4	0	0	0
Other	13 (28)	3	2	3	3	2
Total	46 (100)	12	16	11	3	4

Table 4. Detailed reasons for classification of the NDAs as category A

Category	Detailed reason	Number of NDAs
A1	The clinical data package was inappropriate	10
A2	The clinical study design was inappropriate	2

NDA, new drug application.

Table 5. Detailed reasons for classification of the NDAs as category B

Category	Detailed reason	Number of NDAs
B1	Deficiency in the evidence of an optimal dosage regimen	12
B2	Deficiency in the evidence of maximum dose	2
B3	Efficacy was not confirmed in a confirmatory trial	7

NDA, new drug application.

Table 6. Main changes in the additional clinical study undertaken

Changes in clinical study	Numbers (%)
Study design	3 (6)
Change from crossover design to parallel group design	1
Change from unblinded trial to double-blind trial	2
Study subjects	4 (9)
Limitation of study subjects	2
Alteration of study target disease	2
Dosage regimen	11 (23)
Addition of criteria for taking medicine	1
Increase of dose in a confirmatory trial	3
Addition of a low-dose group	3
Addition of a high-dose group	1
Alteration of dose escalation method	2
Alteration of dose adjustment method	1
Duration of exposure	4 (9)
Extension of duration	3
Shortening of duration	1
Control group	13 (28)
Addition of placebo group (include pseudo-placebo)	8
Alteration of control drug	4
Addition of control drug	1
Endpoint	12 (26)
Alteration of primary endpoint	9
Alteration of methods to evaluate efficacy	3
Total	47 (100)

inappropriate. An additional trial was conducted to confirm superiority over placebo (or pseudo-placebo) and non-inferiority against an existing drug. For lansoprazole and celecoxib, non-inferiority was confirmed against an existing drug in the confirmatory

trial. For duloxetine hydrochloride, the dose determined in the clinical studies (under 30 mg) was inappropriate. In the cases of lansoprazole, celecoxib and duloxetine hydrochloride, additional clinical trials were conducted to confirm the efficacy with higher doses than used in the clinical trials reported in the initial NDA. These results showed that it was necessary to carefully determine the dosage regimen in clinical trials to include the starting dose, the dose titration method and the maximum dose. All available information should be analysed when a clinical trial is planned.

In all the NDAs identified as category B, additional clinical studies were performed to obtain the approval after the initial application was withdrawn or after some 'proposed indications and usage' or 'proposed dosage and administration' in this application were removed. When the trial sponsors designed these additional studies, it was possible to consider points raised in the regulatory review. Thus, the study designs were more likely to be appropriate. Therefore, we compared the designs of these studies in the latter application with those of the studies in the initial application.

Changes to the initial studies made in the additional clinical studies are shown in Table 6. Changes relating to 'control group' were most common (28%) followed by 'endpoint' (26%) and 'dosage regimens' (23%).

Of the changes relating to 'control group', 'addition of placebo group' was the most common (8/13). This might be attributed to the timing of clinical studies that were submitted in the initial NDAs with most of these studies being performed before 2000. In Japan, placebo-controlled clinical trials were not performed actively before 2000 because of concerns about the ethics of such trials.¹⁸ However, the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E10 guideline¹⁹ was issued in 2001 and use of placebo gradually became more common for certain circumstances.¹⁸ Therefore, setting a placebo group is unlikely to be a problem at present because of the E10 guideline, and control groups were set appropriately in these trials.

Among the actions related to 'endpoint', there were problems with 'alteration of primary endpoint' (9/12) and 'alteration of methods to evaluate efficacy' (3/12). The latter was also related to the primary endpoint. Most of the remedial actions related to changes in primary endpoint to allow more objective evaluation of outcome. These observations suggest that it is important to ensure that the methods used allowed objective evaluation of efficacy.

WHAT IS NEW AND CONCLUSION

Our results indicate the importance of careful determination of the optimal dosage regimen and the choice of objective endpoints in clinical trials. Further, it is important to establish a clear strategy for generating the clinical data package, to include careful design of clinical trials on the basis of the nature of the target disease and target population. For drugs marketed in Japan, there is a need to include sufficient numbers of Japanese patients in the trials. We recommend that regulatory authorities be consulted early to identify likely problems.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Details of the NDAs classified into Category A and B.

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