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Post-Marketing Change in Dosage and Administrations of FDA-Approved Drugs Between 2000 and 2017

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ABSTRACT

Purpose: Relevant information on the change in dosage in the post-marketing stage would be useful in considering future clinical development strategies. Therefore, we investigated the content and timing of post-marketing dosage changes using labeling information for New Molecular Entities (NMEs) approved by the FDA.

Methods: We compiled a list of NMEs approved by the FDA between January 1, 2000, and December 31, 2017, using the FDA's website, and the descriptions of the section "dosage and administration" in the latest labeling as of December 31, 2018, were compared with that for the initial approval for each drug. The time required for the change in dosage for the main patient population was estimated using survival analysis.

Results: Of the 432 NMEs, 425 (98%) were evaluable. Dosage changes in the initially indicated populations occurred in 178 NMEs (42%). The time required for the change in dosage was shorter for recently approved drugs. Dosage changes for the main patient population, patients with renal/hepatic impairment, and pediatric/adolescent patients accounted for 23%, 27%, and 24% of the total 275 changes, respectively. For dose-related labeling change for the main patients, the earliest change occurred 1 year after approval, and some drugs took more than 10 years before the change.

Conclusion: Over 40% of NMEs approved by the FDA after 2000 underwent a change in dosage after marketing, and over half of the total changes were for special populations. It is necessary to consider ways to accelerate the establishment of appropriate dosages for special populations after marketing.

Keywords: Drug dosage and administration; Dose-related labeling change; Post-marketing changes; Dosage changes; New molecular entities

INTRODUCTION

The recommended dosage and administration of pharmaceutical products is decided by the regulatory authority based on clinical trial data and other information in terms of both efficacy and safety [1]. However, information obtained from clinical trials before approval may not adequately reflect actual clinical situations because clinical trials are conducted under limited conditions. Therefore, dosage and administration, considered adequate at the time of approval, may later be inadequate based on new information obtained after marketing and revised to be more appropriate [2]. In addition, a new dosage may be set for some of the indicated populations excluded from the initial clinical trials (e.g., children, pregnant women) or for a condition that was not examined (e.g., combination with other drugs that affect metabolism). Approximately 20% (73 of 354 drugs) of New Molecular Entities (NMEs) approved by the US Food and Drug Administration (FDA) between 1980 and 1999 underwent a change in dosage after marketing [3].

In a previous report, changes in dosage and administration after marketing were classified into two categories: increase and decrease in dosage, and it was shown that there were more dose reductions. Since clinical trials are conducted in limited situations, it is easily conceivable that new information regarding safety will be obtained after marketing, in which drugs are used in more practical and unrestricted situations, which leads to a reduction in dose for safety reasons. However, there is no mention in the report of what trends were observed in changes in dosage in special populations, often excluded from general clinical trials.

For some drugs, clinical trials for special populations are conducted in parallel with those for the main populations from the early stage

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of clinical development, and dosage and administration for the special populations are set at the time of initial approval. However, it is often not realistic to study the recommended dosage for all special populations from the early stage of development, considering the recent increase in the cost of new drug development. At the same time, it would be preferable to seek appropriate dosage information, including that for special populations, as soon as possible, even in the post-marketing stage. Thus, relevant information on the change in dosage in the post-marketing stage, such as the purpose of the change and the period required for the change, would be useful in considering the clinical development strategy.

The aim of this study was to obtain new knowledge concerning the content and timing of post-marketing dosage changes for existing drugs. For this purpose, we investigated the content and timing of dosage changes using labeling information for NMEs approved by the FDA [4].

MATERIALS AND METHODS

Drugs examined

NMEs approved by the FDA between January 1, 2000, and December 31, 2017, were identified from the Drugs@FDA [5]. Drugs with the same New Drug Application (NDA) number were considered the same drug, and only the first approved drug was used. Drugs for which the dosage and administration were not set numerically at the time of approval (e.g., insulin, ointment), medical gas, and drugs for which the labeling of the initial approval was not available or readable were excluded.

Evaluation of changes in dosage and administration

Labeling for the initial approval of each drug and its latest labeling as of December 31, 2018, were compiled from the Drugs@FDA [5], and the descriptions of the section "dosage and administration" were compared. Only the dosage and administration for the initially approved indication were investigated, and those for newly added indications after initial approval were excluded. If the latest labeling was unavailable from Drugs@FDA, it was retrieved from the company's website.

In this study, "change in dosage" was defined by one of the following:

Change/Addition of dosage: If the dosage set at the initial approval was changed or a new dosage different from that of the initial approval was added, it was defined as a change. This was applied only when the values related to dosage were changed. It was not applied when words such as 'not recommend' or 'avoid' were added or changed. In addition, it included the addition of a new dosage associated with a new formulation (e.g., prolonged release, liquid medicine).

Change/addition of dosage for a part of the indicated populations: If the dosage for a special population among the initially indicated population was set, added, or changed, it was defined as a change.

Change/addition of administration method: If administration methods were newly set, added, or changed, it was defined as a change. (e.g., when starting dose or maintenance dose was newly set, or when the dose was required to be gradually decreased with the withdrawal of the drug)

Change/addition of administration conditions: If the conditions for administration were newly set, added, or changed under specific conditions (e.g., concomitant use of CYP inhibitors, occurrence of adverse drug reactions), it was defined as a change.

Classification of changes in dosage and administration

Drugs with changes in dosage and administration were classified into the following four categories: If there were multiple changes for the same drug, they were counted separately. If the same change was made multiple times at different times, it was counted as one. In addition, if one change corresponded to multiple changes, it was counted as one*.

Change in dosage in main patient population: If dosage and administration for the initially indicated main patient population was changed, it was classified under this category.

Change in dosage in special populations: If dosage and administration for special populations within the initially indicated population was newly set or changed, it was classified under this category. ('pediatric/adolescent patients', 'pregnant patients' and 'patients with renal/hepatic impairment')

Dosage modification for drug interactions: If dosage and administration for concomitant use of drugs that affect the metabolism of the target drug (e.g., CYP inhibitors) were newly set or changed, they were classified under this category.

Dosage modification for adverse drug reactions: If dosage and administration when adverse drug reactions occurred were newly set or changed, it was classified under this category.

*If dosage and administration of drug interactions or adverse drug reactions for special populations were changed, it was classified under this category and not as a 'special population'.

Time required for changes in dosage

The time required for the change in dosage and administration was defined as the difference between "Approval Date" in "Drug Approval Reports by Month" (Drugs@FDA) and "Action Date" in the revised label for which the dosage and administration were changed. If a revised labeling was unavailable from Drugs@FDA and the time of change could not be specified, the latest available labeling was used as the labeling at the time of change.

Analyses

Descriptive analysis of dosage changes by approval year, ATC classification, and content: Initial drug approval years were grouped into four periods (2000–2004, 2005–2009, 2010–2013, 2014–2017), and the percentage of drugs with dosage change and the time required for the change were evaluated by period. In addition, NMEs were classified by ATC classification [6] and the change in dosage and administration were evaluated by ATC classification. The content of dosage change was examined by the four categories.

Time required for dosage change for main patient population: In order to illustrate the drug characteristics in relation to the time required for the change in dosage and administration for the main patient populations, drugs corresponding to four therapeutic categories [6] (psychoneurotic disorder, infectious diseases, lifestyle diseases, and cancer) were selected, and Kaplan-Meier survival curves of changes in dosage and administration were constructed and compared. (Refer to the Appendix for details on therapeutic

categories.)

All analyses were performed using Microsoft® Excel® 2016 (Microsoft Corporation) and StatsDirect® (version 3.0.182, StatsDirect Ltd., Altrincham, Cheshire, UK).

RESULTS

Forty-two NMEs were approved by the FDA between 2000 and 2017. After excluding seven drugs for which the dosage and administration were not set numerically in the labeling or of which the labeling at the initial approval was not available or readable, we used 425 drugs for the analysis. Among them, 178 drugs (42%) underwent changes in dosage and administration during the study period.

Examination by approval year

Table 1 illustrates the percentage of NMEs with change in dosage by four periods for the initial approval of the drugs. The time required for the change in dosage became shorter for recently approved drugs, and the median time for drugs approved in 2014–2017 was less than 30% of that for drugs approved in 2000–2004.

Table 1: Percentage of NMEs with change in dose-related label information, by approval epoch and Range of market time by epoch.

Approval epoch	No. of NMEs	No. of changed NMEs	Percentage of epoch (%)	Market time (median days)	Minimum (days)	Maximum (days)
2000-2004	117	59	50%	2493	211	6318
2005-2009	92	45	49%	2044	184	4449
2010-2013	97	46	47%	1292	224	2800
2014-2017	119	28	24%	680	196	1471

Examination by ATC classification

As shown in Table 2, the percentage of NMEs with changes in dosage differed widely among the different ATC classes.

Table 2: Raw percentage of NMEs with change in dose-related label information, by ATC class.

	No. of NMEs	No. of changed NMEs	Percentage of class (%)
A	55	20	36
B	24	8	33
C	28	11	39
D	13	0	0
G	21	2	10
H	11	1	9
J	59	36	61
L	85	53	62
M	10	3	30
N	56	30	54
P	7	1	14
R	15	6	40
S	14	0	0
V	32	7	22

Note: Five drugs that meet multiple criteria in the ATC class, however there is no dosage or administration that changes

Examination by content of change

As illustrated in Figure 1, dose-related labeling changes for the main patient populations and special populations accounted for 23% and 52% of the total 275 changes, respectively. Drugs in ATC Class J accounted for about 42% (n=25/60) of dosage changes in pediatric patients, and 40% (n=25/62) of dosage changes in Class J were for pediatric patients. All dosage changes for pregnant patients were associated with anti-HIV drugs (Class J). Drugs in Class L accounted for 46% and 88% (n=34/74, 23/26) of dosage changes in patients with renal/hepatic impairment and dose modification for adverse reactions, and a high percentage (n=34/90, 23/90) of dosage changes in Class L were for patients with renal/hepatic impairment and dose modification for adverse reactions. Dose modification for drug interactions occurred more often in drugs in Classes L and N (n=15/43, 9/43).

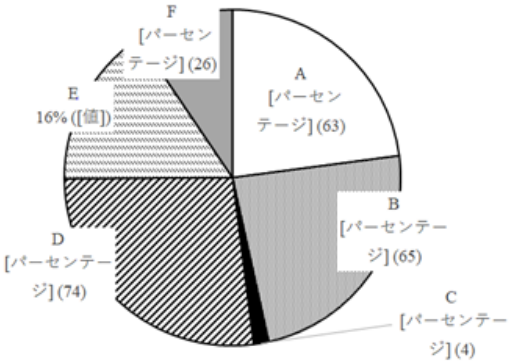

Figure 1: The breakdown of change the dosage and administration. A; Main patients, B; Pediatric or Adolescent patients, C; Pregnant patients, D; Patients with renal or hepatic impairment, E; Dosage Modification for drug interactions, F; Dosage Modification for adverse drug reaction.

Examination of time for dosage change in the main patients

As illustrated in Figures 2 and 3, more drugs in therapeutic categories in psychoneurotic disorders, lifestyle diseases, and cancer underwent dosage changes compared to those in infectious diseases. For some infectious disease drugs, dose-related labeling change for the main patients occurred approximately 1 year after approval, which was earlier than that for other drugs. In contrast, dose-related labeling changes for the main patients in drugs for lifestyle diseases did not occur 10 years after approval.

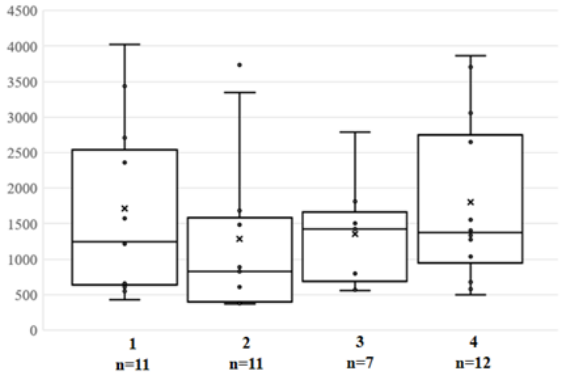

Figure 2: The time required to change the dosage and administration of the main patient by therapeutic category of drugs. 1; Agents affecting nervous system, 2; Infectious disease drug, 3; lifestyle disease (hypertension, dyslipidemia, diabetes, gout), 4; Anti-cancer drug.

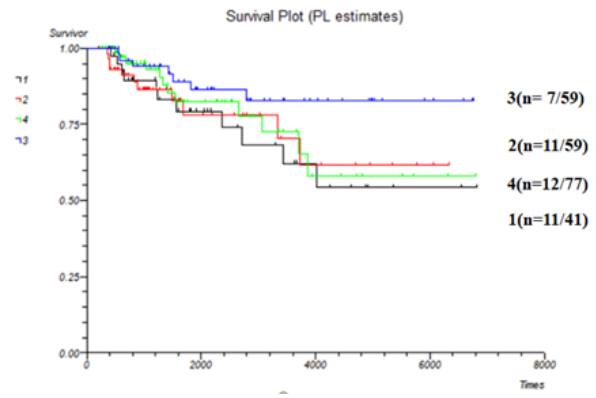

Figure 3: The time required to change the dosage and administration of the main patient by therapeutic category of drugs. 1; Agents affecting nervous system (N03, N04, N05, N06) 2; Infectious disease drug (J01-07, R05) 3; lifestyle disease (hypertension, dyslipidemia, diabetes, gout) (A10, B01, C02, C03, C04, C07-10, M04) 4; Anti-cancer drug (L01, L02, V10).

DISCUSSION

The present study showed that over 40% of NMEs approved by the FDA after 2000 underwent a dosage change by the end of 2018. Nowadays, it has become relatively easy to obtain information useful for drug development, for example, clinical trial data related to similar drugs [7] and post-marketing safety information [8,9]. However, some drugs underwent a dose-related labeling change for the main patient populations, even though they had received regulatory approval based on relatively large pivotal studies. Therefore, the information obtained from clinical trials before approval is still limited.

Regarding the time required for the dosage change, recently approved drugs showed a relatively shorter period compared to older drugs. This was consistent with a previous report, and we understand that the time to dosage change has become shorter for drugs approved recently.

Special populations are often excluded from general clinical trials. Therefore, it was expected that the dosage for special populations had not been set at the initial approval and was often newly set or changed after marketing based on additional clinical trials and this study showed that (Figure 1). For pediatric dosage change, the Pediatric Rule in 1998 and the Pediatric Research Equity Act in 2003 must have contributed to the increase [10].

It has been suggested that dosage changes in pediatric patients are closely linked to drugs in ATC class J. According to a research report regarding the reasons for hospitalization in children aged 17 years and younger in the US in 2012, respiratory diagnoses were the most common specific conditions. In addition, skin and subcutaneous tissue infections and urinary tract infections are also among the top 10 specific reasons [11]. Infectious diseases accounted for the major reasons for hospitalization among children, and many drugs in Class J underwent a dose-related labeling change in pediatric patients. This is considered an indication of pharmaceutical companies meeting medical needs for effective and safe dosage information for children.

All the dose-related labeling changes for pregnant patients were made with anti-HIV drugs (Class J), aimed at preventing transmission of HIV to newborns [12]. In general, drug use in pregnant patients is avoided, and often excluded from clinical trials. As for anti-HIV drugs, due to their efficacy not only for pregnant patients but also for their newborns, dosage for pregnant patients was set reflecting the high medical needs.

Dose-related labeling changes for patients with renal/hepatic impairment and dose modification for adverse reactions were made more with drugs in ATC Class L, and a high percentage of dosage change were for patients with renal/hepatic impairment and dose modification for adverse reactions. Patients receiving drugs in Class L may often be associated with impairment of organ function, which may worsen with progression of the disease. In addition, many anticancer drugs are highly toxic. Therefore, it is considered that dosage change for patients with renal/hepatic impairment and dose modification for adverse reactions occurred more frequently for drugs in Class L [13]. We believe that the present study provides the expected results.

Dose modification for drug interactions occurred more often in drugs in ATC Classes L and N. Drugs in Classes L and N are often administered for a long period and are used in conjunction with other drugs for the treatment of coexisting diseases. Therefore, more emphasis has been placed on dose modification for drug interactions for these drugs compared to other drugs that are administered in a short period or can be easily changed to similar drugs. Many drugs in Classes D and S have vague definitions and descriptions of dosage (e.g., one drop in the affected eye(s) once daily), which is why no drugs in these classes underwent dosage change after their initial approval.

Dose-related labeling changes in pediatric/adolescent patients, and patients with renal/hepatic impairment, who are often excluded from clinical trials, accounted for more than half of the total changes, as expected. At the same time, it was an unexpected result that dosage changes for the main patient population, who should have been a target population in clinical trials, accounted for more than 20% of the total changes. In general, it takes several years to complete a clinical trial. Therefore, it may take several years to change the dosage and administration in the labeling. Regarding the time for dosage change for the main patient population, some of the drugs for infectious diseases underwent a change in less than one year after the initial approval, and the median time for the change was the shortest among drugs in different therapeutic areas. In clinical trials of drugs for infectious diseases, clinical efficacy based on clinical symptoms or laboratory data is often set as the primary endpoint. These require a shorter time to be evaluated compared to other endpoints used for other categories. This may account for the relatively short period of dose-related labeling changes in this therapeutic category compared to others.

There are few drugs for lifestyle diseases that undergo dosage change more than five years after the initial approval. In these therapeutic areas, similar drugs, generic drugs, and fixed-combination products have been actively developed. From the viewpoint of clinical development strategy in the pharmaceutical industry, it might be less profitable if they invest time and money in activities for dosage change, and their resources might be devoted to the development of combination products or other new drugs instead of considering life-cycle management of the original drug over a period of time after approval. On the other hand, there were some drugs affecting the nervous system and anti-cancer drugs that underwent a change approximately 11 years after the initial approval. It might be beneficial that drugs in these therapeutic categories continue to

be examined for a more appropriate dosage for a long term, since these drugs are administered over a long period and cannot be easily changed to similar drugs.

In the present study, a considerable number of recently approved NMEs still underwent a change in dosage after marketing. It is suggested that the goal of clinical development be not to obtain initial approval, but to continue activities toward more appropriate use of a drug after its marketing. Although it is not feasible to eliminate the possibility that some problems occur and are associated with an unpredictable risk after marketing, it is important to adequately collect and analyze information on possible risks during the clinical trial to prepare an appropriate risk management plan.

However, regarding predictable changes in dosage, such as new setting of dosage and administration in special populations, it might be effective to plan a forward-looking strategy for changing the dosage after marketing from the early stage of clinical development. Currently, it is relatively easy to obtain information on clinical trials of similar drugs and post-marketing safety information, and it is important for pharmaceutical industries to make use of such information and data in order to proceed with drug development under limited resources.

A limitation of the present study was that we could not accurately determine the time for dosage change for some drugs because we used the labeling information published on the FDA website and past labeling information for some drugs was not available. However, missing labeling was not disproportionate with respect to approval year and ATC class; therefore, we believe that the obtained results would not be affected. In this study, we did not investigate the reasons for and background to the dosage change in the main patient population. It would be our future task to illuminate them to obtain new knowledge for future new drug development.

CONCLUSION

Over 40 % of NMEs approved by the FDA after 2000 underwent a change in dosage after marketing. This shows that safety and efficacy information obtained from clinical trials before approval is still limited. The present study showed that dose-related labeling changes in special populations accounted for over half of the total changes. Although it is useful that dosage for special populations, which are often excluded from clinical trials, were newly set or changed after marketing, it is necessary to consider ways to accelerate the establishment of appropriate dosages for special populations after marketing.

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