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PHASE III STUDIES

Significant differences on submission lag following regulation reform for registration of novel therapeutic drugs in Taiwan

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Summary
Drug lag, which delays patients' access to medicinal products, is typically associated with pharmaceutical regulations. To shorten drug lag, health authorities may establish new policies to liberalize the regulations, a step that is important in countries, such as Taiwan, with consumer demand for imported novel therapeutic agents. Taiwan's government enacted Articles 38–1 and 38–2 of Regulations for Registration of Medicinal Products to relax the regulatory barriers for new drug submission, thus conditionally exempting the requirement for the Certificate of Pharmaceutical Product (CPP). This study examined whether the enacted regulations reduce submission lag by analyzing the time gap of submission between Taiwan and the United States during 2014–2017. The results indicated that the enacted regulations substantially affected submission lag. Submission lag was significantly shorter for applications not requiring a CPP than those requiring one CPP, which in turn was significantly shorter than those requiring two CPPs. This conclusion can be applied to biological, chemical, non-orphan, and oncology drugs and also applications filed by subsidiary companies, but not orphan drugs and applications filed by contract agents. Among applications requiring one CPP, oncology drugs showed the shortest submission lag. Certain factors, such as clinical studies recruiting over-threshold Taiwanese participants and those performed before the submission of new drug application in the United States, may shorten submission lag. In summary, this study justifies the policy of the exemption from CPP requirements, which supports the hypothesis that relaxing regulatory barriers can reduce submission lag in Taiwan.

Keywords Submission lag · Regulation reform · Certificate of Pharmaceutical Product · Clinical study · Article 38–1 · Article 38–2

Introduction

New drug development is an important process affecting pharmaceutical profiles. Drug lag, which determines how soon a patient can access new medicinal products, is a serious issue in Taiwan [1]. By definition, drug lag is a broad term referring to any delay in making a drug available in market to the patients [2]. It may comprise certain distinctive lag times at various time points, such as time required for completing clinical studies, submitting new drug application (NDA) to health authorities, and reviewing the submission dossiers [3].

A more specific index of drug lag, namely submission lag, can be used to compute the time interval between the submission time of a drug in a given country and that in another country, typically the United States (US) or European Union (EU) countries [4, 5]. Various demanding and complicated regulatory requirements are usually the major reasons for delay in the submission the product applications [2]. Submission lag aids in a practical comparison of the degree of drug delay in different attributes of pharmaceutical profile. Another potential advantage of using submission lag is that it can be employed as a reference by health authorities who relax regulatory barriers by enacting new policies. This enables earlier submission of the applications, which in turn aids in reducing the waiting time of patients to access the required medicinal products. For instance, in Japan, drug lag is a serious issue: the delay from development to market availability is often longer in Japan than in other pharmaceutically advanced countries [5]. Japanese regulatory agency thus encourages sponsors to use global clinical studies to

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shorten submission lag [4], according to the notification of the basic principle of global clinical studies [6].

Enactment of regulatory policies has been employed by the Taiwan Food and Drug Administration (FDA), and that successfully improves pharmaceutical features in various aspects, such as dossier quality, review time, and clinical study. For example, redundant review of poor filing dossiers has been reduced by launching a refuse-to-file procedure [7], review time has been shortened by abbreviating the dossiers for drug master file applications accepted by advanced countries [8]. Most importantly, in terms of the association to the liberalization of submission lag, the number of clinical study applications for novel therapeutic agents successfully increases after the enactment of the Article 38-1 of Regulations for Registration of Medicinal Products [9], which denotes that approval from 10 designated advanced countries (A10 countries [10]) is not mandatory if Taiwanese participants fulfill the minimum threshold in the relevant clinical studies. However, whether submission lag in Taiwan can be improved through liberalization of regulatory policy remains unknown. Thus, the validity of submission lag as a substantial variable for indexing the degree of drug lag warrants investigation.

Before 2001, the timing of the submission in Taiwan was influenced by several criteria, including (i) a local clinical study comprising at least 40 Taiwanese participants and (ii) up to three Certificates of Pharmaceutical Product (CPPs) obtained from advanced countries [11, 12]. To reduce the requirement of local trial and CPPs, Taiwan's government announced a series of policies, beginning in 2001, all of which finally led to the enactment of Articles 38–1 and 38-2 of Regulations for Registration of Medicinal Products. The enacted regulations indicate the development of multinational clinical studies must involve a minimum threshold of Taiwanese participants; however, a local clinical study is not mandatory. Article 38–1 exempts the requirement of two CPPs at NDA submission if two clinical studies (i.e., phases I and III or phases II and III) are performed. Article 38-2 exempts the requirement of one CPP at NDA submission if one clinical study is performed.

Data on submission lag in Taiwan is unavailable. The present study is the first to examine the hypothesis that the liberalization of regulatory barriers affects submission lag. Here, submission lags for imported novel therapeutic drugs during 2014–2017 were compared between Taiwan and the US, in terms of license holders, structural features, disease designations, and therapeutic areas. The current results provide not only Taiwan's experience regarding the outcomes of the CPP reduction policy but also some insight into the relationship between submission lags and pharmaceutical regulations.

Materials and methods

Data source

Data analyses were performed based on the novel therapeutic applications by foreign developers; these applications were submitted to Taiwan FDA between January 1, 2014 and December 31, 2017. The 4-year timeframe was employed to ensure that the representative applications could effectively reflect the outcome of policy reform. As a product development is a time-consuming process, a long gap between the announcement of reformed policy and the beginning of this study period (i.e., 13 years after the announcement of the policy in 2001) was necessary. Biosimilar products and products with new indications, new formulations, new strengths, new dosage forms, and new administration routes were all excluded in the present study. During data analysis, a product with multiple strengths was counted as one application.

Application characteristics

Application characteristics were sorted and summarized in terms of license holders, structural features, disease designations, and therapeutic areas. License holders were categorized as subsidiary companies (affiliated to a headquarters) and contract agents (under contract with an originated license holder). Structural features were classified into two categories: chemical or biological drugs. Disease designation was categorized as orphan and non-orphan drug for rare and non-rare diseases, respectively. The therapeutic area of an active ingredient followed the Anatomical Therapeutic Classification (ATC) code according to the World Health Organization classification [13].

Clinical development strategy analysis

To analyze applications, local and global clinical studies related to the proposed indication were retrospectively identified in the development process. For studies recruiting Taiwanese participants, the clinical stages and participant numbers were collected to evaluate whether the application fulfilled Articles 38-1 and 38-2. Fulfilling Article 38-1 requires two clinical studies (i.e., phases I and III or II and III) with the number of Taiwanese participants fulfilling a minimum threshold (i.e., 10, 20, and 80 for phases I, II, and III,

respectively). If any study had a number of Taiwanese participants below the threshold, whether that study fulfilled Article 38-2 criteria was evaluated. Article 38-2 only requires one clinical study in which Taiwanese participants must fulfill one of the following criteria: (1) at least 10 in a phase I study, (2) at least 20 or more than 10% of total participants in a phase II study, (3) at least 80 or more than 10% of total participants in a phase III study, (4) at least 30 or 5% in a study of more than 200 participants in total, and (5) at least 10 in a study less than 200 participants in total. For fulfilling (4) and (5), multinational phase III studies involving any A10 countries [10] are required, and the results are used to support NDAs filing to the US FDA or European agency.

Submission lag analysis

To analyze the submission lag relative to the US, the application submission date to the US FDA was searched from the US website (drugs@FDA: FDA Approved Drug Products). If an application submission date was not posted on the website, submission lag was estimated by subtracting the approval date from 360 days for standard review and from 180 days for accelerated review. Submission lag was calculated from the time difference in the application submission date to the US FDA and its submission date to the Taiwan FDA (i.e., Taiwan FDA date minus US FDA date). Applications not approved in the US were excluded. The submission lag was analyzed according to whether Articles 38-1 and 38-2 were fulfilled or unfulfilled in terms of the following characteristics: license holder, structural feature, disease designation, and therapeutic area. In addition, submission lag was further analyzed to determine whether applications fulfilling Article 38-1 or 38-2 showed differences with clinical studies conducted before or after NDA submission in the US FDA. The Wilcoxon rank-sum test was employed to determine the statistical significance (considered $p < 0.05$) between groups. The software R project (Ri 386 3.3.3) was used for data analysis. The results were presented by the medium with percentile values at 10th, 25th, 75th, and 90th percentiles calculated for each set of data.

Results

Characteristic summary of analyzed applications

From January 1, 2014 to December 31, 2017, a total of 139 applications were submitted for novel therapeutic agents (Table 1). Of the 139 applications, 16 were not approved in the US; thus, 123 applications were included. The major characteristic license holders, structural features, and disease designations were subsidiary companies (78.9%), chemical drugs (65.0%), and non-orphan drugs (87.8%), respectively. The major therapeutic areas were distributed in antineoplastic and immunomodulating agents (denoted L according to ATC code: 41.5%), systemic anti-infective agents (denoted J according to ATC code: 15.4%), and gastrointestinal and metabolic agents (denoted A according to ATC code: 13.0%).

Clinical development strategy of analyzed applications

Of the included 123 applications, 5 (4.1%), 18 (14.6%), and 63 (51.2%) for phase I, II, and III clinical studies included Taiwanese participants, respectively (Table 2). Moreover, 5 (4.1%) phase I, 9 (7.3%) phase II, and 29 (23.6%) phase III clinical studies fulfilled the patient number thresholds (i.e., 10, 20, and 80 for phase I, II and III clinical studies, respectively). Of these 123 applications, four phase II and III studies, but none of the phase I and III studies, fulfilled with the Article 38-1 criteria. Among the studies not fulfilling the threshold, 1 (0.8%) phase II and 3 (2.4%) phase III studies fulfilled Article 38-2 criteria. Taken together, of the 123 applications, 38 (30.9%) fulfilled Article 38-2 and 81 (65.9%) fulfilled neither Article 38-1 nor Article 38-2.

Submission lag of applications fulfilling and unfulfilling Articles 38–1 and 38–2 and timing of clinical study initiation

The median submission lag was 553 days between Taiwan FDA and US FDA over a 4-year period. An average of 564 days was noted for those applications fulfilling Article 38-1 or 38-2. Applications fulfilling Article 38-1 (median = 118 days) showed a significantly reduced lag compared with those fulfilling Article 38-2 (median = 374 days; $p < 0.05$; Fig. 1) and not fulfilling Article 38-1 or 38-2 (median = 707 days; $p < 0.001$). Similarly, applications fulfilling Article 38-2 demonstrated a significant difference ($p < 0.001$) relative to those not fulfilling Articles 38-1 and 38-2. Subanalysis of Article 38-2 applications revealed that submission lag further decreased (median = 209 days) for those initiating their clinical studies before the US NDA submission. By contrast, Article 38-2 applications initiating their clinical studies after US NDA submission showed an increased lag (median = 998 days). Significant difference ($p < 0.001$) was demonstrated in the timings of clinical study initiation.

Table 1 Characteristic summary of analyzed applications

Characteristics	Number of applications ($n = 123$; %)
New chemical entity/new biologic applications submitted in Taiwan	
2014	24 (19%)
2015	39 (32%)
2016	37 (30%)
2017	23 (19%)
License holder	
Contract agent	26 (21.1%)
Subsidiary company	97 (78.9%)
Structural feature	
Biological drug	43 (35.0%)
Chemical drug	80 (65.0%)
Disease designation	
Orphan drug	15 (12.2%)
Non-orphan drug	108 (87.8%)
Therapeutic area	
A (Alimentary tract and metabolism)	16 (13.0%)
B (Blood and blood-forming organs)	12 (9.8%)
C (Cardiovascular system)	6 (4.9%)
D (Dermatologicals)	3 (2.4%)
G (Genitourinary system and sex hormones)	1 (0.8%)
H (Systemic hormonal preparations)	1 (0.8%)
J (Anti-infectives for systemic use)	19 (15.4%)
L (Antineoplastic and immunomodulating agents)	51 (41.5%)
M (Musculoskeletal system)	1 (0.8%)
N (Nervous system)	6 (4.9%)
P (Antiparasitic products)	0 (0%)
R (Respiratory system)	2 (1.6%)
S (Sensory organs)	0 (0%)
V (Various)	5 (4.0%)

Submission lag of applications in terms of characteristic analysis

Submission lag of applications on characteristic analysis in terms of license holders, structural features, and disease designations are described subsequently (Fig. 2). Submission lag demonstrated significant differences between the two license holder types, contract agents and subsidiary companies (median = 1306 and 475 days, respectively; $p < 0.001$). Submission lag demonstrated differences between the two types of structural features, biological and chemical products (median = 471 vs. 721 days; $p < 0.05$). Submission lag demonstrated meaningful differences between two categories for disease designation, orphan and non-orphan drugs (median = 1083 vs. 504 days; $p < 0.01$).

Submission lag of applications in terms of license holder

Applications fulfilling Article 38-1 were all filed by subsidiary companies (Fig. 3). Among the subsidiary company applications, the submission lags were significantly shorter for applications fulfilling Article 38–1 (median = 118 days) than for applications fulfilling Article 38-2 (median = 351 days; $p < 0.05$) and not fulfilling Article 38-1 or 38-2 (median = 553 days; $p < 0.01$). Moreover, significantly shorter lags were noted for applications fulfilling

Table 2 Clinical development summary of analyzed applications

Characteristics	Applications (%)
Clinical study recruiting Taiwanese participants	
Phase I	5 (4.1%)
< 10 Taiwanese participants	0 (0%)
≥ 10 Taiwanese participants	5 (4.1%)
Phase II[a]	18 (14.6%)
< 20 Taiwanese participants and not fulfilling Article 38-2	8 (6.5%)
< 20 Taiwanese participants and fulfilling Article 38-2	1 (0.8%)
≥ 20 Taiwanese participants	9 (7.3%)
Phase III[a]	63 (51.2%)
< 80 Taiwanese participants and not fulfilling Article 38-2	31 (25.2%)
< 80 Taiwanese participants and fulfilling Article 38-2	3 (2.4%)
≥ 80 Taiwanese participants	29 (23.6%)
Clinical development in relation with Articles 38-1 and 38-2[a,b]	
Applications fulfilling Article 38-1	4 (3.3%)
Applications fulfilling Article 38-2	38 (30.9%)
Applications not fulfilling Article 38-1 or 38-2	81 (65.9%)

[a] Article 38-2 is referred to Regulations for Registration of Medicinal Products. Article 38-2 requires one clinical study with the number of Taiwanese participants fulfilling one of the following criteria: (1) at least 10 in a phase I study, (2) at least 20 or more than 10% of total participants in a phase II study, (3) at least 80 or more than 10% of total participants in a phase III study, (4) at least 30 or 5% in a study more than 200 participants, and (5) at least 10 in a study less than 200 participants. For fulfilling (4) and (5), multi-national phase III studies involving any A10 countries [10] are required, and the results are used to support NDAs filing to the US FDA or European agency

[b] Article 38-1 is referred to Regulations for Registration of Medicinal Products. Article 38-1 requires two clinical studies (i.e., phases I and III or II and III) with the number of Taiwanese participants fulfilling a minimum threshold (i.e., 10, 20, and 80 for phases I, II, and III, respectively)

Article 38-2 compared with those not fulfilling Article 38-1 or 38-2 ($p < 0.01$). By contrast, among applications submitted by contract agents, the differences between applications fulfilling Article 38-2 and those not fulfilling Article 38-1 or 38-2 were nonsignificant (median = 724 vs. 1556 days, $p > 0.05$). Regarding Article 38-2-fulfilling applications, the two license holder types demonstrated no difference. However, for applications not fulfilling Article 38-1 or 38-2 products, applications submitted by contract agents had a longer lag (median = 1556 days) than did those submitted by subsidiary companies (median = 553 days; $p < 0.01$).

Submission lag of applications in terms of structural feature

For biological products, significantly shorter lags were reported for applications fulfilling Article 38-2 (median = 389 days) relative to those not fulfilling Article 38-1 or 38–2 (median = 514 days; $p < 0.05$; Fig. 4). A similar trend was observed for chemical products: applications fulfilling Article 38-2 demonstrated significantly shorter lags compared with those not fulfilling Article 38-1 or 38-2 (median = 359 vs. 902 days; $p < 0.01$). Regarding applications fulfilling Article 38-2, no differences were noted between two structural features. By contrast, for applications not fulfilling Article 38-1 or 38-2, chemical products showed longer lag times than did biological products (median = 902 vs. 514 days; $p < 0.05$).

Submission lag of applications in terms of disease designation

Applications fulfilling Article 38–1 were all non-orphan drugs (Fig. 5). Among non-orphan drugs, applications fulfilling Article 38-1 (median = 118 days) demonstrated significantly shorter lags compared with those fulfilling Article 38-2 (median = 359 days; $p < 0.05$) and not fulfilling Article 38-1 or 38-2 (median = 645 days; $p < 0.01$). Moreover, significantly shorter lags were noted for applications fulfilling Article 38-

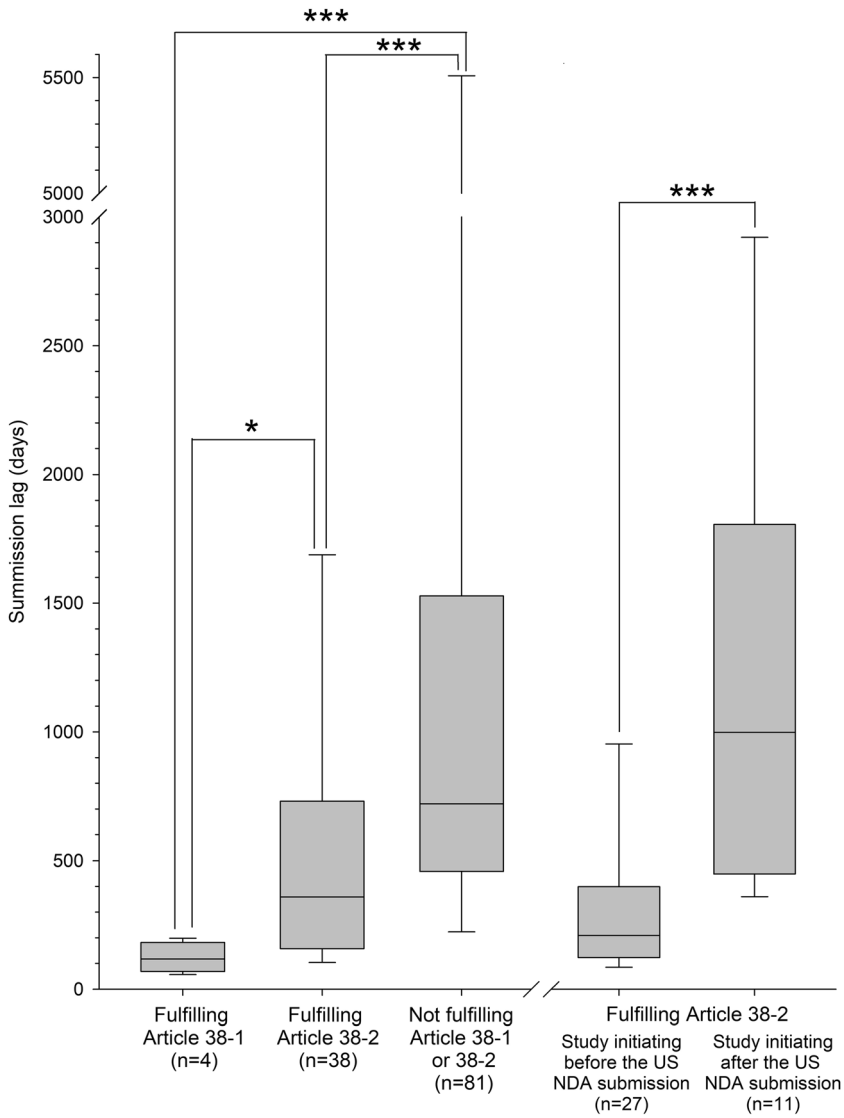

Fig. 1 Submission lag of applications fulfilling and not fulfilling Articles 38-1 and 38-2 and submission lag of applications fulfilling Article 38-2 by timeing of clinical study initiation. Articles 38-1 and 38-2 are referred to Regulations for Registration of Medicinal Products. The top, middle, and bottom in the box plot indicate the 75th percentile, median, and the 25th percentile, respectively. Error bars indicate the 10th and 90th percentiles. *$P < 0.05$. ***$P < 0.001$

2 relative to those not fulfilling Article 38-1 or 38-2 ($p < 0.01$). By contrast, the differences between applications of fulfilling Article 38-2 and those not fulfilling Article 38-1 or 38-2 were nonsignificant among orphan drugs (median = 811 vs. 1237 days, $p > 0.05$). Regarding applications not fulfilling Article 38-1 or 38-2, orphan and non-orphan drugs demonstrated no difference (median = 1237 vs. 645 days; $p > 0.05$).

Submission lag of applications in terms of therapeutic area

Figure 6 illustrated L (median = 472 days) showed significantly shorter lag compared with A (median = 1042 days; $p < 0.01$), drugs for nervous system (median = 1376 days; $p < 0.01$), and drugs for various uses (median = 6047 days; $p < 0.05$). J had significantly shorter submission lags relative to A (median = 448 vs. 1042 days; $p < 0.05$). Regarding three major areas (A, J, and L), significant differences between applications fulfilling Article 38-2 and those not fulfilling Article 38-1 or 38-2 were found in L (median = 222 vs. 516; $p < 0.001$; Fig. 7); however, for A and J no differences were noted between two types. Moreover, L demonstrated the lowest median (222 days) among applications fulfilling Article 38-2. For applications not fulfilling Article 38-1 or 38-2, A and L showed significant difference (median = 3564 vs. 516 days; $p < 0.01$).

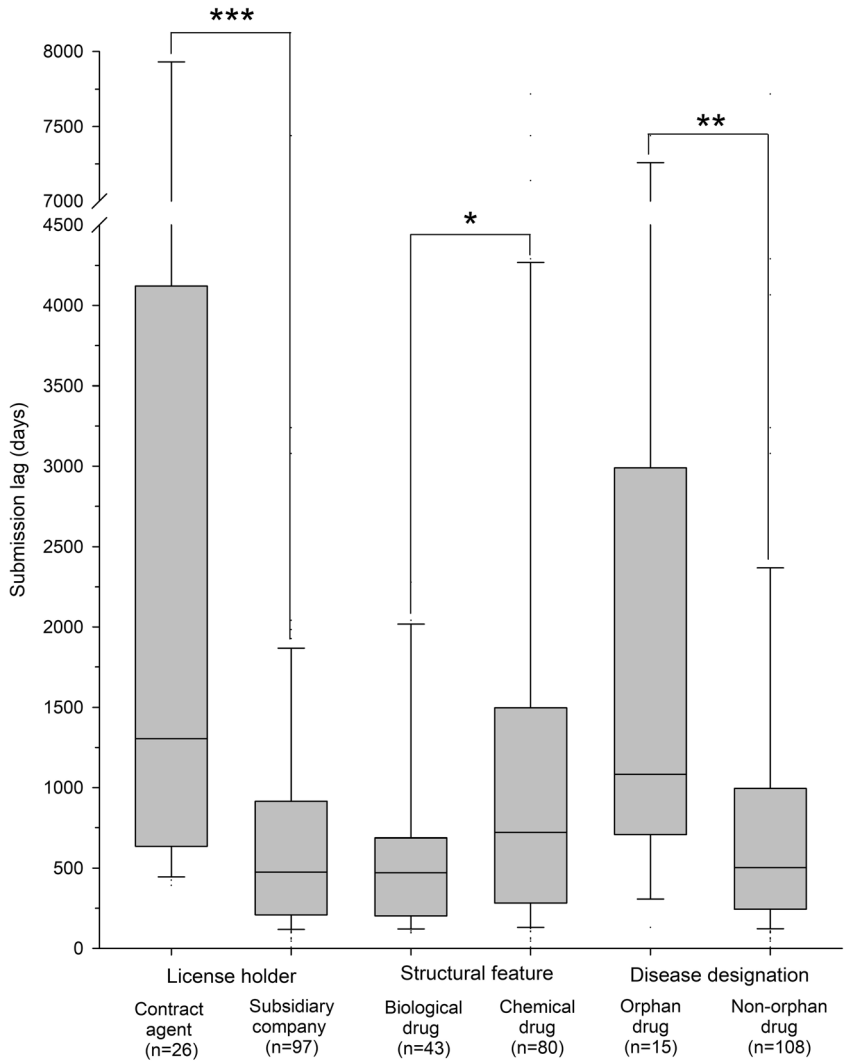

Fig. 2 Submission lag of applications on characteristic analysis in terms of license holder, structural feature and disease designation. The top, middle, and bottom in the box plot indicate the 75th percentile, median, and the 25th percentile, respectively. Error bars indicate the 10th and 90th percentiles. *$P < 0.05$. **$P < 0.01$. ***$P < 0.001$

Discussion

In general, drug lag delays patients' early access to medicinal products, a serious issue for both the pharmaceutical industry and health authorities. By definition, delay in approval of a drug in certain country after its approval in other country is caused by review and submission lags [2]. Submission lag is a major concern for imported products in Taiwan because, before June 2001, up to three CPPs were a prerequisite for an NDA package [12, 14]; however, the information on the exact submission lag remains unknown. A drug lag study in Taiwan revealed an average approval lag of 30.5 months (i.e., 915 days) during 1996–2002 after assessing 80 new drugs [1]; the authors defined drug lag measurement by using the differences in approval lag between Taiwan and the first country the drug was approved in. If a review lag is absent, the approval lag may substantially reflect submission lag. Thus, the average approval lag of 915 days refers to an average submission lag against the country the drugs were first approved in for 1996–2002. In short, to demonstrate the importance of drug lag in Taiwan, previous studies have employed average time rather than median time as the present study did, which may be more practical in submission lag analysis [15, 16].

To evaluate the efficacy of drug regulation reform, the present study compared the submission lag of NDA submissions to the Taiwan FDA with those to the US FDA during 2014–2017. For those fulfilling CPP reduction criteria, a median of 553 days over a 4-year period and an average of 18.6 months (i.e., 564 days) improved the lag time.

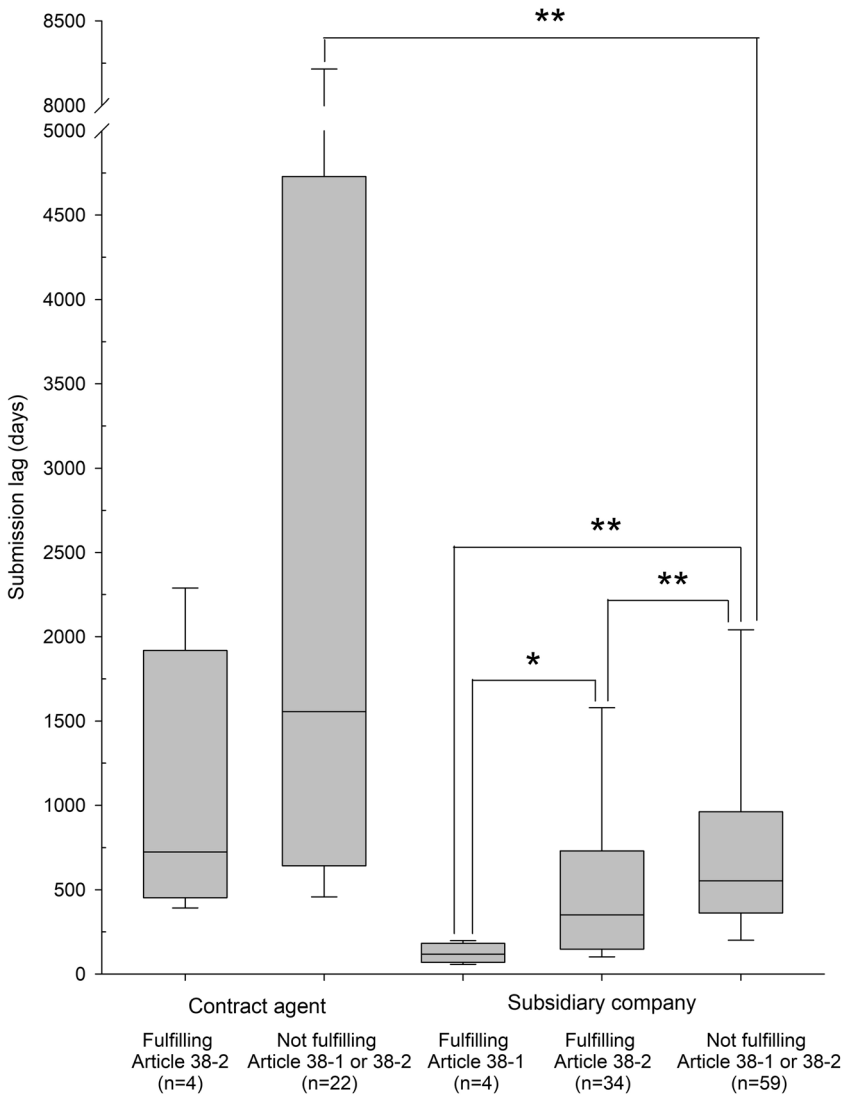

Fig. 3 Submission lag of applications fulfilling and not fulfilling Articles 38-1 and 38-2 in terms of license holder-contract agent and subsidiary company. Articles 38-1 and 38-2 are referred to Regulations for Regiatration of Medicinal Products. The top, middle, and bottom in the box plot indicate the 75th percentile, median, and the 25th percentile, respectively. Error bars indicate the 10th and 90th percentiles. *$P < 0.05$. **$P < 0.01$

Furthermore, submission lag was significantly shortened for applications fulfilling Article 38-1 (CPP not required) or 38-2 (one CPP required) than those not (two CPPs required; Fig. 1). In particular, CPP-waived applications had the shortest submission lag during the study period. Similar profiles were obtained consistently in analyses of different characteristics such as biological, chemical drugs, non-orphan drugs, and oncology drugs (Figs. 4, 5 and 7) and applications filed by subsidiary company (Fig. 3). It highlights the role of the enacted regulations by health authorities in adjusting the pharmaceutical product profiles.

To apply for registration in Taiwan for an imported product, local companies are either a subsidiary company or a contract agent. The results showed the aforementioned profiles referred only to applications submitted by subsidiary companies, not contract agents (Fig. 3). In addition, the percentage of applications that satisfied the reformed regulations was lower for contract agents than that for subsidiary companies (38/97 for subsidiary company vs. 4/22 for contract agent). Regarding the applications requiring two CPPs (not fulfilling CPP reduction criteria), a significantly long submission lag was observed for contract agents. Taken together (Fig. 2), an evident difference was noted among license holders; contract agents appeared to have relatively more difficulty in not only satisfying the reformed criteria but also preparing the dossiers or documents for submission.

According to the structural feature analysis, the applications requiring one CPP criteria had significantly shorter

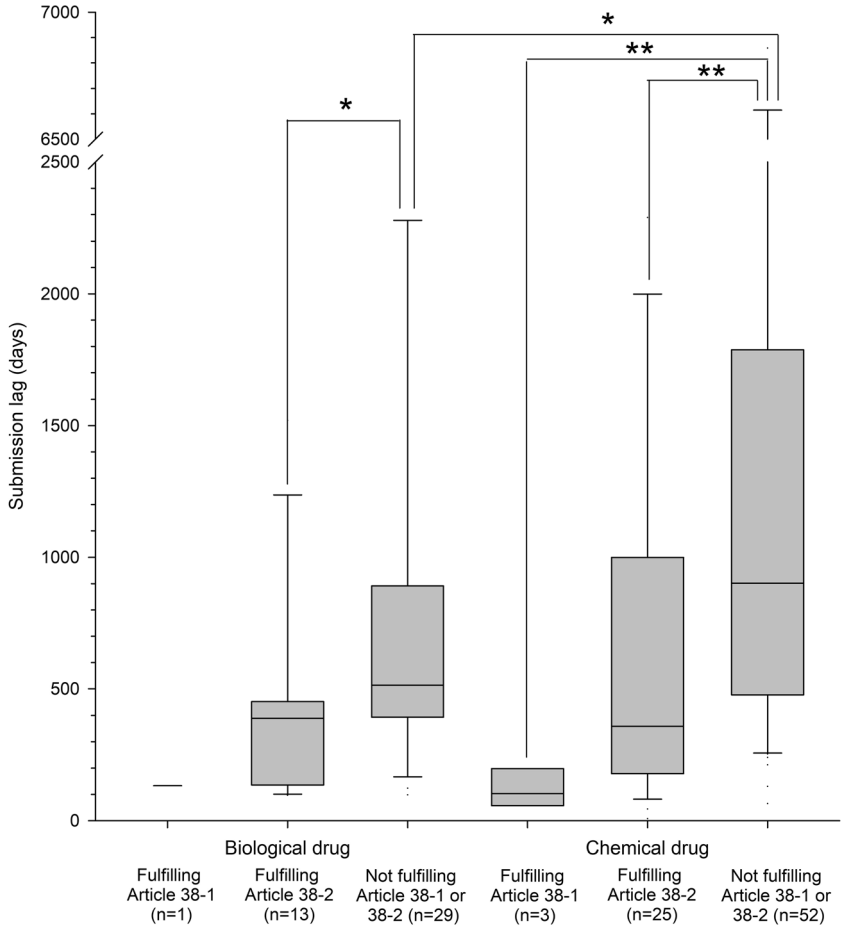

Fig. 4 Submission lag of applications fulfilling and not fulfilling Articles 38-1 and 38-2 in terms of structural feature-biological and chemical drugs. Articles 38-1 and 38-2 are referred to Regulations for Regiatration of Medicinal Products. The top, middle, and bottom in the box plot indicate the 75th percentile, median, and the 25th percentile, respectively. Error bars indicate the 10th and 90th percentiles. *$P < 0.05$. **$P < 0.01$

submission lag than did those requiring two CPPs for submission for both biological and chemical drugs (Fig. 4). Similar percentage of biological and chemical drug applications fulfilled the reform regulations (biological [14/43] vs. chemical [28/80]). In general, a significantly longer lag was observed for chemical drugs (Fig. 2) because chemical drug applications not fulfilling the reformed regulations had notably longer submission lag than did those for biological drugs in the same category.

In the context of disease designations, orphan drugs, especially those requiring two CPPs, had significantly longer submission lag than did non-orphan drugs (Fig. 5). Non-orphan drugs appeared to be profiled, with significant differences in lag time, as follows: CPP required = zero < one < two. Among the 15 orphan drug applications submitted by contract agents, 7 demonstrated long submission lag. In addition, most orphan drug applications (14/15) were those not fulfilling reform regulations. This observation may attributable to the number of orphan drug-medicated patients being limited. Therefore, in such cases, satisfying the criterion of recruiting Taiwanese participants over a threshold in a given global clinical study is difficult [17].

Submission lag considerably decreased, but not for most of the applications (65.9%, Table 2). Only 4.1%, 14.6% and 51.2% of the drugs were launched in the phase I, II and III studies, respectively. In approximately half of the phase II and III studies enrolling Taiwanese participants, the CPP reduction criteria were not met. Most foreign developers did not appear to consider Taiwanese participants as their patients. Studies that considered these participants did not completely incorporate the reformed regulations in their development strategies. For instance, some of them recruited Taiwanese participants at a number less than the threshold and failed to comply with Article 38-2 criteria. A study reported that only approximately 12% of Taiwanese people were willing to participate the clinical studies [18], similar to the findings in the US (11%) [19]; thus, Taiwanese participants not being

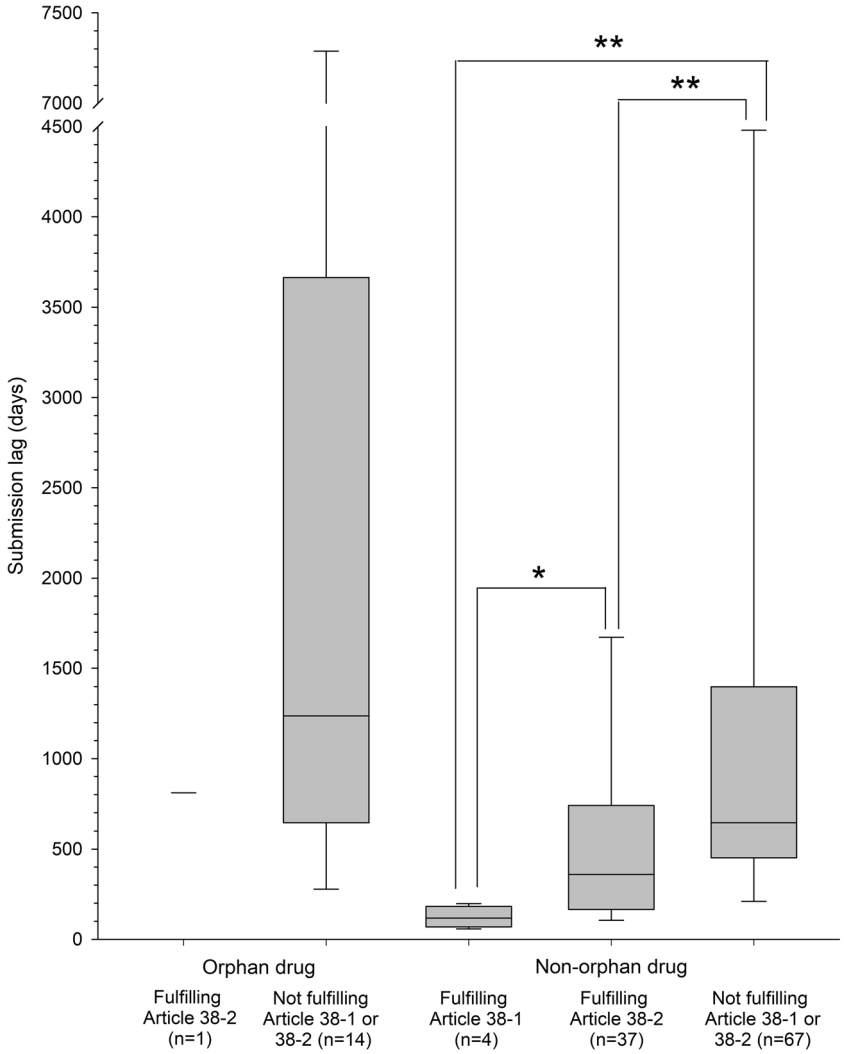

Fig. 5 Submission lag of applications fulfilling and not fulfilling Articles 38-1 and 38-2 in terms of disease designation-orphan and non-orphan drugs. Articles 38-1 and 38-2 are referred to Regulations for Registration of Medicinal Products. The top, middle, and bottom in the box plot indicate the 75th percentile, median, and the 25th percentile, respectively. Error bars indicate the 10th and 90th percentiles. *$P < 0.05$. **$P < 0.01$

recruited in the global studies was not the primary reason for submission lag. Enrolling Taiwanese participants is just an incentive to reduce the drug lag in Taiwan, but not a mandatory requisite for NDA. Conducting clinical studies in Taiwan and recruiting sufficient Taiwanese participants can be difficult, because of competition from the neighboring countries, such as Japan (the third largest pharmaceutical market globally; the Taiwanese market occupies only approximately 6% of Japanese market).

In the present study, the lag could be varied according to the therapeutic area. Oncology drugs not only accounted for the largest quantity (Table 1) but also for a significantly shorter submission lag (median 472 days) compared with that for metabolism and nervous system (Fig. 6). In addition, new regulations led to the shortest submission lag when only one CPP was required, given the lowest median lag (222 days, Fig. 7), which apparently was lower than the median for contract agents (724 days), subsidiary companies (351 days), biological drugs (389 days), chemical drugs (359 days), orphan drugs (811 days), non-orphan drugs (359 days), metabolic drugs (998 days), and anti-infective drugs (351 days; Figs. 3, 4, 5 and 7). This implied that oncology drugs elicit a relatively great incentive for the developers to fulfill reformed regulations in Taiwan. In addition, a lower median lag of a given drug may be associated with its high unmet medical need; this means that patients can buy the drug on the market earlier.

Note the regulations in Taiwan have been in place since 2001, however whether the drugs can be benefited is highly

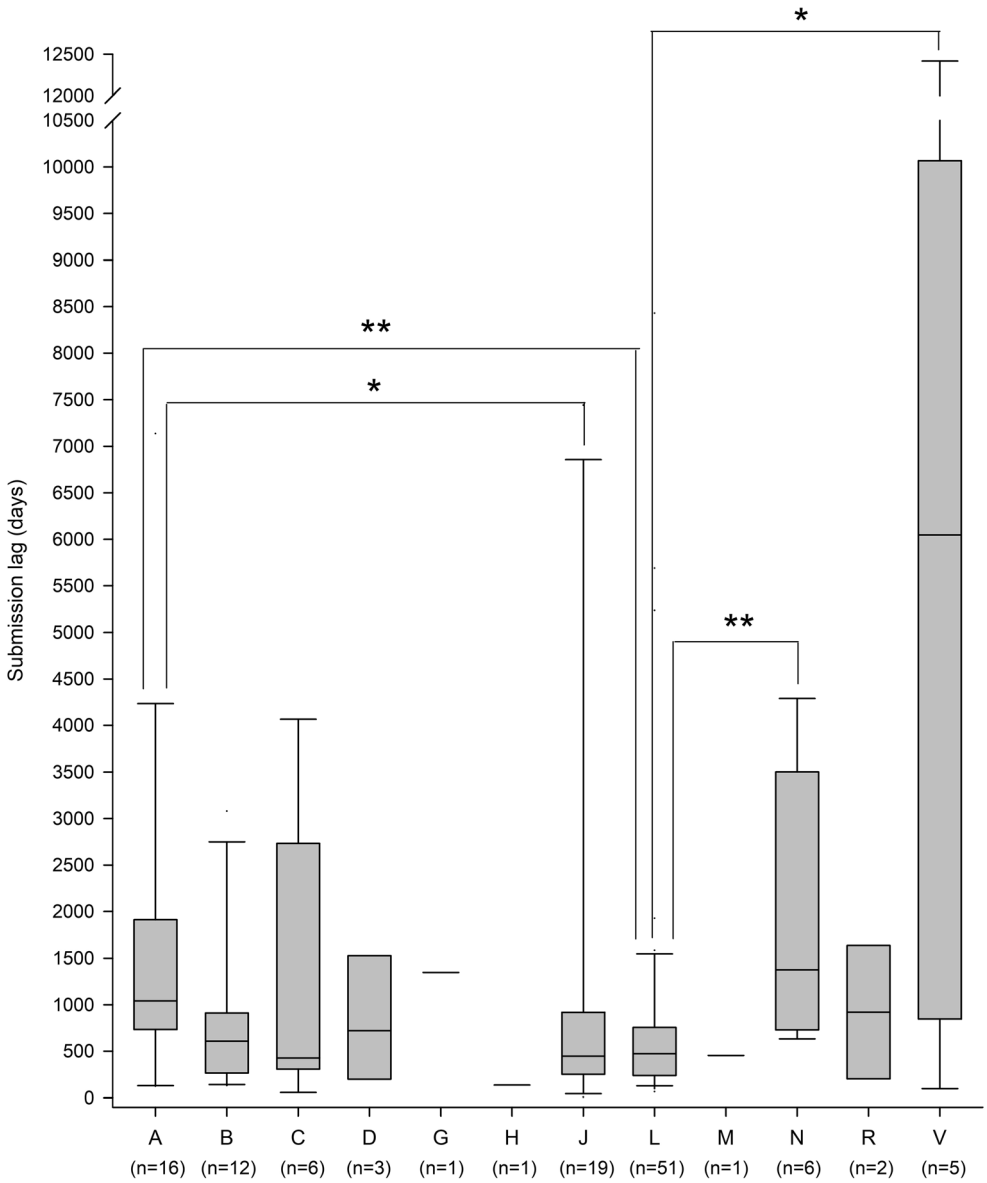

Fig. 6 Submission lag distribution in terms of therapeutic area. A: alimentary tract and metabolism; B: blood and blood forming organs; C: cardiovascular system; D: dermatologicals; G: genitourinary system and sex hormones; H: systemic hormonal preparations; J: anti-infectives for system use; L: antineoplastic and immunomodulating agents; M: musculoskeletal system; N: nervous system; R: respiratory system; V: various. The top, middle, and bottom in the box plot indicate the 75th percentile, median, and the 25th percentile, respectively. Error bars indicate the 10th and 90th percentiles. *$P < 0.05$. **$P < 0.01$

determined by their fulfillment of the regulations. For example, in Taiwan the submission lag of oncology drugs fulfilling reformed regulations was 222 days, shorter than that of Japan (281 days) [20], whereas the overall submission lag of oncology drugs (472 days) is apparently longer than that of Japan.

Here, submission lag for the applications starting the clinical study before the US NDA submission was significantly shorter than for those not doing so, highlighting that the timing of initiation of clinical studies may affect submission lag [21]. Therefore, the clinical development strategies, particularly the timing of initiating the clinical studies, are keys to reducing submission lag. A similar phenomenon was noted in Japan, wherein average submission lag for new chemical drugs decreased to <8 months during 2011–2014 [18].

Finally, the current results can be compared with those in Japan, which has a long history of considerable drug lag [5]. Notably, although the causes of their submission lag differed, the remedial approaches of Taiwan and Japan were similar. In Taiwan, the health authority replaced the foreign approval requirement with participation of Taiwanese people in global clinical studies; this successfully reduced submission lag—an incentive for overseas pharmaceutical sectors to conduct clinical studies for novel therapeutic agents

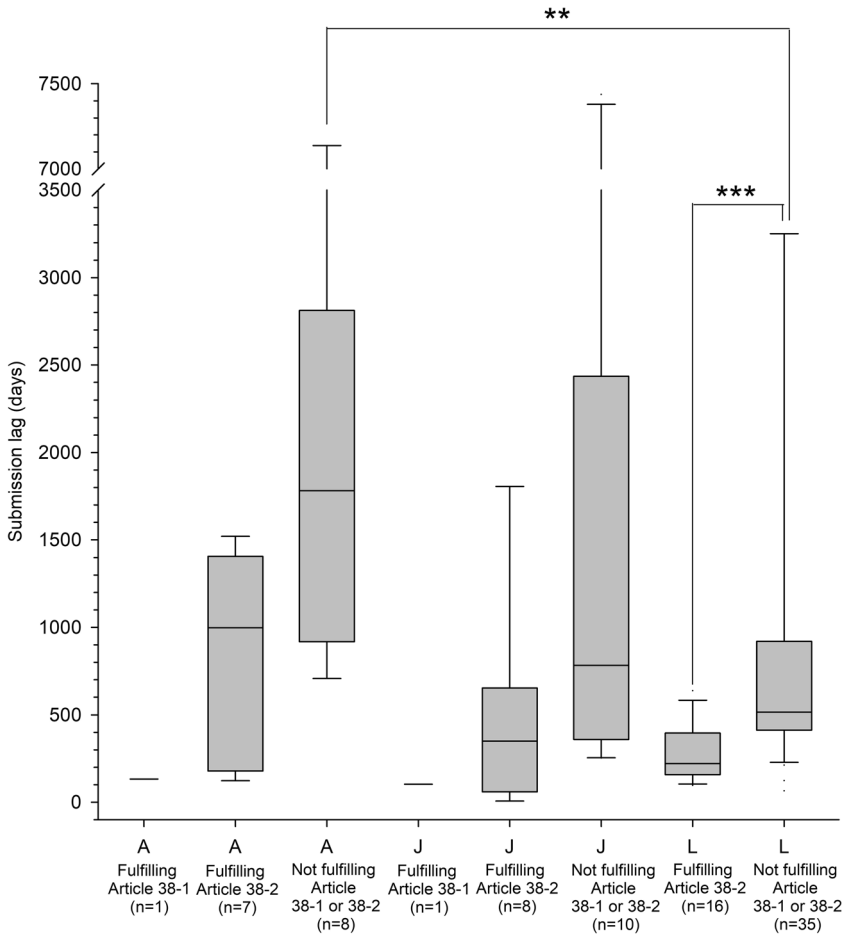

Fig. 7 Submission lag of applications fulfilling and not fulfilling Articles 38-1 and 38-2 in terms of therapeutic area- A, J and L. Articles 38-1 and 38-2 are referred to Regulations for Regiatration of Medicinal Products. A (alimentary tract and metabolism), J (anti-infectives for systemic use) and L (antineoplastic and immunomodulatory agent). The top, middle, and bottom in the box plot indicate the 75th percentile, median, and the 25th percentile, respectively. Error bars indicate the 10th and 90th percentiles. $^{**}P < 0.01$. $^{***}P < 0.001$

in Taiwan [9]. A long submission lag was noted in Japan because a Japanese clinical study is a prerequisite for the NDA package [5]. Thus, for improving submission lag in Japan, the Japanese regulatory agency encourages applicants to use global clinical studies to recruit Japanese patients; this action would also address the ethnic issue to satisfy local requirements. This action would be an effective way to remedy the situation that approximately 60% approved drugs in the US and EU countries did not launch clinical studies in Japan [22].

Conclusions

In summary, the present study demonstrated that the reformed policy in Taiwan substantially influences submission lag. Submission lag of applications not requiring a CPP (Article 38-1) was shorter than that of those requiring one CPP (Article 38-2), which in turn was shorter than that of those requiring two CPPs. This principle was applied to biological, chemical, non-orphan, and oncology drugs and applications filed by subsidiary companies, but not orphan drugs and applications filed by contract agents. Among applications requiring one CPP, oncology drugs showed the shortest submission lag. Certain factors, including clinical studies recruiting over-threshold Taiwanese participants and timing of initiation of clinical studies, may be applied to shorten the submission lag.

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Compliance with ethical standards

Conflict of interest I-Chen Sun declares that she has no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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