



Application Profile of Full and Abbreviated Dossiers for Drug Master File: An Experience of Taiwan

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Background: In Taiwan, drug master file (DMF) serves as a useful database regarding the quality of active pharmaceutical ingredients in which both full and abbreviated dossiers can be submitted. Moreover, mandatory substances have been implemented recently, yet the details of the outcome remain unrevealed. **Methods:** This study aims to compare these two application profiles and their reviewing outcomes. Data were collected from the new submissions of both full and abbreviated dossiers completed between January 1 and December 31 of 2014 by the Center for Drug Evaluation, Taiwan. **Results:** The top two countries for DMF applications were India and China in both full and abbreviated dossier types. Drugs acting in the alimentary tract and metabolism, cardiovascular system, anti-infectives, and nervous system were the most prevalent. Majority of the abbreviated dossiers provided certification of suitability to the monographs of the European Pharmacopoeia rather than other types of documentation among the eligible documents applying for mandatory applications in which the acceptance rate was higher than that of full dossiers. **Conclusions:** Our data not only suggests that submission of abbreviated dossier is more effective to receive regulatory approval, but also demonstrates that the policy of health authority is a key in the improvement of reviewing process.

Key words: Active pharmaceutical ingredient, drug master file, abbreviated dossier, full dossier, mandatory substances

INTRODUCTION

The quality of active pharmaceutical ingredients (APIs) is a determinant of safety and efficacy of drug product for therapeutic use. For decades, certain advanced countries have established a system, drug master file (DMF), to provide confidential information applicable to APIs.^{1,2} In general, a DMF contains the technical documents regarding chemistry, manufacturing, controls, packaging, and stability for an API.^{1,2} In the United States, a DMF submission would not initiate the review process unless the new drug application (NDA) or abbreviated NDA (ANDA) is in relation to a specified DMF, where approval or disapproval of this DMF is not given.¹

In contrast to the United States, the DMF system in Taiwan had not been established until October 1, 2009.³ In the first few years (i.e., 2009–2013), the submission of a DMF is voluntary. After submission, the reviewing process operates immediately because it is less relevant to NDA and ANDA when the

DMF policy begins. For an accepted DMF application, a certificate is issued, which, in turn, will allow for increasing the reimbursement pricing of a generic product.⁴ The purpose of DMF submission aims to ensure the quality of APIs. It operates initially in a retrospective manner; however, recent years a prospective approach is employed.⁵

The format of DMF technical documents requires complete dossiers (i.e., full dossiers) as listed in the common technical document of the International Conference on Harmonization.⁶ In considering some of DMF applications were already approved by advanced countries, the health authority of Taiwan establishes an alternative pathway since 2011.⁷ The DMF application can be in an abbreviated format with a prerequisite of the API approval from the countries recognized by the health authority of Taiwan, based on the reliability of these countries in performing the evaluation of quality, safety, and efficacy for medicinal products.⁸

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In later amendment, the policy has shifted to link product approval for certain active substances in Taiwan since May 2013.⁵ Namely, for certain APIs the DMF filing become mandatory and associated with product applications (i.e., NDA or ANDA). Ten pharmacologically active ingredients are listed in the mandatory DMFs, including acetaminophen, cefaclor, cefazolin (sodium), dextromethorphan HBr, diclofenac sodium, gliclazide, metformin HCl, risperidone, tamsulosin HCl, and valproic acid. Furthermore, to ensure the above mentioned APIs' quality in all products, this requirement has been extended to currently marketed products.

In fact, policy reform of health authority is sometimes associated with the application profile.⁹ Previously in a longitudinal manner, we analyzed the association between application profile and acceptance rate in corresponding to that the DMF filing has been launched since 2009.¹⁰ The author further demonstrated the effectiveness of simplified application by comparing the reviewing outcomes between the two dossier type-based applications.¹¹ To reveal the influences in recent advancement of DMF policies, including abbreviated and mandatory submissions, this study aims to investigate the distribution of DMF applications in countries of manufacturers, therapeutic areas, and status of ten mandatory substances.

METHODS

The data of this study were collected from the new submissions of both full and abbreviated dossiers, in which the evaluation was completed between January 1 and December 31, 2014 by the Center for Drug Evaluation, Taiwan. As the enactment of the mandatory substance was announced on May 2013. Thus the data of the next year, that is, 2014, were analyzed in this study. The application profiles were then analyzed by country of API manufacturer and active substance utility according to dossier type. For active substance utility, it was assessed according to the anatomical therapeutic classification (ATC) system of the World Health Organization, in which ATC code for the API was assigned.¹² The corresponding ATC code for the mandatory substances was also analyzed.

For mandatory substances, evaluation of the outcome included the acceptance/rejection rates and the document type for the validity of abbreviated dossiers which were sorted out by dossier type. For the accepted documents for eligibility of abbreviated submission, they are required for indicating the API source and manufacturer by the ten advanced countries. They can be certificate of pharmaceutical product (CPP), certificate of good manufacturing practice. Alternatively, API can be approved by certification of suitability to the monographs of the European Pharmacopoeia (CEP) (issued by European Directorate from the Quality of Medicines and

Healthcare [EDQM]) given that the CEP provides a high-quality level of standards in qualifying the drug substance.¹³

RESULTS

1. From January 1 to December 31 of 2014 (i.e., the study period), 732 new applications were completed; 517 (70.6%) of those were applied for full dossiers and 215 (29.4%) for abbreviated dossiers. Table 1 shows that the distribution of application by country (i.e., the sites of products manufactured). In full dossier type applications, India (229, 44.3%), China (224, 43.3%), Italy (15, 2.9%), and Spain (9, 1.7%) were accounted for the top four countries. Similarly, India (99, 46.0%), China (41, 19.1%), Italy (27, 12.6%), and Spain (14, 6.5%) were the top four countries for abbreviated dossiers with the same order compared to

Table 1: Country distribution of manufacturers

Country [#]	Full dossier, n (%)	Abbreviated dossier, n (%)
Brazil	1 (0.2)	0
China	224 (43.3)	41 (19.1)
Czech Republic	4 (0.7)	2 (0.9)
Demark	0	2 (0.9)
Finland	1 (0.2)	0
France	0	5 (2.3)
Germany	1 (0.2)	2 (0.9)
Hungary	1 (0.2)	1 (0.5)
India	229 (44.3)	99 (46.0)
Iran	1 (0.2)	0
Ireland	0	1 (0.5)
Israel	2 (0.4)	1 (0.5)
Italy	15 (2.9)	27 (12.6)
Japan	5 (1.0)	2 (0.9)
Malta	0	1 (0.5)
Mexico	1 (0.2)	1 (0.5)
The Netherlands	1 (0.2)	0
Norway	1 (0.2)	1 (0.5)
Poland	2 (0.4)	0
South Korea	5 (1.0)	2 (0.9)
Spain	9 (1.7)	14 (6.5)
Switzerland	3 (0.6)	10 (4.7)
Thailand	2 (0.4)	0
Turkey	1 (0.2)	0
The United Kingdom	4 (0.8)	1 (0.5)
The United States	4 (0.8)	2 (0.9)
Total	517	215

[#]The countries were presented in an alphabetical order

full dossiers. Note for the full dossiers applications, the first two countries were very closed in numbers (229, 44.3% vs. 224, 43.3%, for India and China, respectively). However, it was not the case for abbreviated dossiers

Table 2: Categorical distribution based on anatomical therapeutic classification

ATC code	Full dossier, n (%)	Abbreviated dossiers, n (%)
A	72 (10.1)	46 (15.2)
B	17 (2.4)	13 (4.3)
C	100 (14.0)	45 (14.9)
D	60 (8.4)	19 (6.3)
G	45 (6.3)	24 (7.9)
H	16 (2.2)	5 (1.7)
J	121 (17.0)	31 (10.3)
L	32 (4.5)	8 (2.6)
M	41 (5.8)	18 (6.0)
N	84 (11.8)	32 (10.6)
P	1 (0.1)	1 (0.3)
R	53 (7.4)	27 (8.9)
S	63 (8.8)	28 (9.3)
V	8 (1.1)	5 (1.7)
Total	713	302

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, excluding sex hormones and insulins; J=Anti-infectives for system use; L=Antineoplastic and immunomodulating agents; M=Musculoskeletal system; N=Nervous system; P=Antiparasitic products, insecticides and repellents; R=Respiratory system; S=Sensory organs; V=Various; ATC=Anatomical therapeutic classification

- The distribution of ATC codes was analyzed for both dossier types [Table 2]. Among 517 full dossiers, 103 substances were given multiple ATC codes, as a result 713 ATC codes were totally collected. Among 215 abbreviated dossiers, 42 substances were given multiple ATC codes, as a result 302 ATC codes were totally collected. In full dossiers, anti-infectives for system use denoted as “J” embodied the largest proportion (121, 17.0%) among all therapeutic categories. Drugs targeting at cardiovascular system denoted as “C” (100, 14.0%) ranked the second largest, followed by drugs targeting at nervous system denoted as “N” (84, 11.8%), and alimentary tract and metabolism denoted as “A” (72, 10.1%). In abbreviated dossiers, “A” (46, 15.2%) was the largest, followed by “C” (45, 14.9%), “N” (32, 10.6%), and “J” (31, 10.3%)
- For the ten mandatory substances, the corresponding ATC code for each substance was listed in Table 3. During the study, 29 applications among 517 full dossiers were related to eight out of ten mandatory substances [Table 3]. Among them, the top three mandatory substances in the decreasing order were metformin, tamsulosin, and acetaminophen. One designated API, cefaclor, showing the lowest application in volume was not accepted. As a whole for the full and mandatory DMF applications, 18 (64.4%) were accepted, but 11 (37.9%) were rejected
- For 215 abbreviated dossiers, 13 applications were associated with five mandatory substances [Table 3], in which the top designated substance was metformin. Since one metformin application was rejected, leading to the accepted and rejected applications were corresponding to

Table 3: Assessment outcomes for the mandatory substances

Mandatory substance (ATC code)	Full dossiers		Abbreviated dossiers		
	Acceptance	Rejection	Acceptance	Rejection	Document type
Acetaminophen (N)	4	2	0	0	-
Cefaclor (J)	1	0	0	0	-
Cefazolin (J)	0	1	1	0	CEP ^a (1)
Dextromethorphan (R, N)	0	0	0	0	-
Diclofenac (D, M, S)	1	1	2	0	CEP (1), CPP of TGA ^b (1)
Gliclazide (A)	1	0	1	0	CEP (1)
Metformin (A)	6	2	7	1	CEP (8)
Risperidone (N)	1	2	0	0	-
Tamsulosin (G)	4	3	0	0	-
Valproic acid (N)	0	0	1	0	CEP (1)
Subtotal (%)	18 (62.1)	11 (37.9)	12 (92.3)	1 (8.3)	CEP (12, 92.3%), CPP of TGA (1, 7.7%)

^aCertificate of suitability to the monographs of the European Pharmacopoeia granted by EDQM, ^bCertificate of a pharmaceutical product granted by Australian agency, TGA. EDQM=European directorate for the quality of medicines and healthcare; TGA=Therapeutic goods administration; ATC=Anatomical therapeutic classification; N=Nervous system; J=Anti-infectives for system use; R=Respiratory system; D=Dermatologicals; M=Musculoskeletal system; S=Sensory organs; A=Alimentary tract and metabolism; G=Genitourinary system and sex hormones; CPP=Certificate of pharmaceutical product

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12 (92.3%) and 1 (7.7%). In the reference documents eligible for abbreviated dossiers, CEP was the most frequently used document (12, 92.3%). Finally, it was noted that only one non-CEP abbreviated dossier was submitted, it was a CPP from Australia health authority.

DISCUSSION

It is important to provide useful information after the operation of any new regulation policy, which is necessary for the health authority for enact new regulation in the future. The present study compared the application profiles and reviewing outcomes between two application types, full and abbreviated dossiers, completed during 2014 in Taiwan. The study results revealed: (i) Country distributive pattern was similar for the full and the abbreviated types of dossier. (ii) In terms of pharmacological profile, the most four dominant ones are the drugs acting on the alimentary tract and metabolism, on cardiovascular system, for systemic anti-infectives, and on nervous system. (iii) For mandatory DMFs, CEP is the majority for the abbreviated document and the abbreviated dossier type had a higher acceptance rate. These findings are discussed as the following.

For the distribution over countries, during 2014, the top two countries of completed applications were India and China in both full and abbreviated dossier types [Table 1]. It reflects the blooming of pharmaceutical industry in Asia in recent years as it is consistent with regulatory status of DMF in Taiwan during 2009–2011 and what was stated in API global sourcing strategies.^{10,14} This result suggests that India and China companies are motivated to seek regulatory approval from other advanced countries, in which India reveals a higher motivation to seek the regulatory approval. Alternatively, it is also possible due to a better quality control than China as showing over two times of the completed applications in obtaining the approval from the advanced countries (46.0% vs. 19.1%). Accordingly, the validity of the documents was also recognized by the Health Authority of Taiwan in abbreviated submission pathway.

In the aspect of pharmacological feature, drugs acting on the alimentary tract and metabolism (A), cardiovascular system (C), anti-infectives (J), and nervous system (N) were the most prevalent in the completed applications; even though, the order of therapeutic classes among full and abbreviated dossiers appeared different. Among 14 classes, the sum of A, C, J, and N were over half of the total applications in both full (52.9%) and abbreviated dossier type (51.0%). It should be addressed that although at present stage the DMF filing is optional for ANDAs (only ten items are compulsory after 2013), it intends to seek a higher drug reimbursement from the National Health Insurance (NHI) in Taiwan. In other words,

these proportions to a degree may reflect the ratio of drugs that apply for the reimbursement. The assumption may be partially supported by the accordance with a previous study in which drugs in A, C, J, and N were the top items and over half items for NHI reimbursed expenditures in 2001.¹⁵ Taken together, these findings may demonstrate an unchanged tendency of the long-term proportion of NHI pharmaceutical products.

It is noted that A, J, and N were the most prevalent ones of ATC codes in Table 2, they were also appeared the largest populations in the mandatory substances as observed in Table 3. The purpose of identifying mandatory substances is to build up a proactive process for obtaining a better quality control, which is employed to NDA/ANDA (in contrast to using a retrospective method for the products already marketed). For doing this, the health authority of Taiwan started with ten substances as listed in Table 3 because they are frequently used in the market.

During the study, 732 DMFs were completed and that were substantially greater than the total applications (471 DMFs) in the first 3 years 2009–2011.⁸ The increase of completed application was associated with the mass submission in 2013 and 2014.¹⁶ Among the completed DMF applications in 2014, it was interesting that applications associated with mandatory substances were <6% (42/732). It could be concluded that the volume of applications apparently did not link directly to the obligatory policy. As the mandatory substances policy started to operate, the applicants may be perspective on the next step policy, in which DMFs would be needed to all products in Taiwan. Afterward, the regulations of requiring APIs technical document were amended in early 2016, which were applicable to all registration of NDA/ANDA.¹⁷ From July 2017, this policy will be implemented to ensure the quality of all pharmacologically active substances instead of designated a few after 1 year of preparation period.¹⁷

For mandatory substances, this study showed the acceptance rate of abbreviated dossiers was higher than that of full dossiers (92.3% vs. 62.1%). The present data were parallel to the previous study regarding total abbreviated and full dossiers (94.9% vs. 64.4%) including mandatory and nonmandatory substances in the same study period.¹¹ Similarly, among the mandatory substances' applications of this study, CEP was demonstrated to be the leading document (92.3%) applied for the abbreviated dossiers. In the same study period (i.e., 2014), our previous study revealed that CEP was also a major document type (95.3%) in abbreviated applications.¹¹ Both results suggest that the CEP predominance is obvious and consistent regardless of the mandatory policy. The reason of this observation could be complicated; however, it can be relevant to that CEP can be applied by an active substance manufacturer and granted by a relative simple EDQM's procedure, whereas a CPP depends on final product quality, preclinical, and clinical data.¹³

CONCLUSION

This study revealed that: (i) India and China companies were motivated to seek regulatory approval from other advanced countries. (ii) Drugs in A, C, J, and N were the top items, which were in a parallel manner correlated with NHI reimbursed expenditures in 2001. (iii) In mandatory substances, the acceptance rate of abbreviated dossiers and the usage of CEP document were similar to the results of the previous study. The data obtained from the present study may provide useful information for the health authority of Taiwan to inspect different characteristics of the DMF applications.

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Conflicts of interest

There are no conflicts of interest.

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