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Advantages of using an abbreviated dossier for drug master file applications in Taiwan

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ABSTRACT

In Taiwan, the quality of active pharmaceutical ingredients is recorded in a drug master file (DMF), the applications for which can be submitted in two dossier types, either full (complete technical information) or abbreviated (partially complete technical information with an approved document issued by developed countries). However, the advantages of the abbreviated approach remain unknown. This study compared full and abbreviated dossier profiles and reviewed their outcomes in acceptance rates and deficiencies leading to rejection. Data were collected from new submissions of both dossier types that were completed in 2014 by the Center for Drug Evaluation, Taiwan. The results revealed that the abbreviated applications took shorter review time and had a higher acceptance rate. Among the eligible types of document for abbreviated applications, Certification of Suitability to the Monographs of the European Pharmacopeia (CEP) was the most frequently used. For categorical deficiencies, both dossier types presented the deficiencies in similar sections leading to rejection, namely Manufacture (3.2.S.2), Control of drug substance (3.2.S.4), and Stability (3.2.S.7). In summary, CEP serves a favorable document for the abbreviated DMF application in which it shortens the review time, increases the acceptance rate, and its deficiencies are similar to those of the full DMF application.

For decades, developed countries have been using established systems for reviewing active pharmaceutical ingredients (APIs) (Drug Master Files: Guideline, 1989; International conference on harmonization technical requirements, 2004), which can be filed through drug master files (DMFs) containing quality information related to the chemistry, manufacturing, and controls of APIs (Drug Master Files: Guideline, 1989). The DMF system in Taiwan was established on October 1, 2009 (Announcement no. 0980363183, 2009). For APIs approved by countries that are recognized by the health authority of Taiwan, DMF applications can be submitted in an abbreviated type (i.e., partially complete technical information with an approved document issued by developed countries). Possible advantages could be that it shortens the review time and improves the acceptance rate (Announcement no. 1001403285, 2011; The designated countries include Australia, 2015).

API approval can be provided through documents indicating the sources and manufacturers of the APIs; examples include a certificate of pharmaceutical products (CPP) and certificate of good manufacturing practice (GMP). Moreover, Certification of Suitability to the Monographs of the European Pharmacopeia (CEP), issued by the European Directorate from the Quality of Medicines and Healthcare (EDQM), can alternatively be used for API approval because this certification provides high-quality standards for qualifying a drug substance (Background & legal framework: Resolution).

The DMF application profile in Taiwan was longitudinally analyzed previously (Sun et al., 2014). In the present study, the author investigated the effectiveness and advantages of using simplified application by cross-sectionally comparing the review outcomes between the full and abbreviated dossier applications. The results may provide useful information for health authorities to justify the necessity of using an abbreviated dossier for DMF applications.

1. Distribution of full and abbreviated dossier applications

The author collected new DMF submissions in both full and abbreviated applications completely evaluated by Taiwan's Center for Drug Evaluation between January 1 and December 31, 2014. The

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evaluation process generally proceeds in three rounds for both dossier types. In the first round, the application is thoroughly evaluated; for dossiers identified as containing insufficient or inadequate information, a supplementary document is requested. The second round begins after the applicant responds to the first inquiry; if the queried issue remains unresolved, the applicant is allowed to provide further supplementary documentation before a final decision (i.e., completed evaluation) is made. An acceptance certificate is issued for an application accepted after the evaluation process has been completed, whereas a rejection letter addressing the deficiencies is issued for an application that remains unaccepted in the third round. The application profile was then analyzed according to the dossier types, review time, acceptance and rejection rates, eligible document types for abbreviated dossiers, and deficiencies leading to rejection.

During the study period, 732 new applications were completed: 517 (70.6%) full dossiers and 215 (29.4%) abbreviated dossiers. Among the full dossiers, 333 (64.4%) DMF applications were accepted, 184 (35.6%) were rejected, and 174 ± 98 (mean ± standard deviation) calendar days were required for reviewing these dossiers. Among the abbreviated dossiers, 204 (94.9%) DMF applications were accepted, 11 (5.1%) were rejected, and 73 ± 53 calendar days were required for reviewing these dossiers (Table 1).

Certain factors must be considered when interpreting the results of the present study. First, the DMF applications investigated in this study might not be inclusive because the application data were obtained for only 1 year (i.e., 2014); nevertheless, the total number of applications in 2014 was almost two-fold compared with that in 2009–2011 (Sun et al., 2014). Second, because the time required for the review process varied considerably, time might be a confounding factor in interpreting the data.

2. Documents eligible for abbreviated dossier application

Table 2 presents the reference document types that are eligible for submitting abbreviated dossiers. CEP was the most used reference document type (205, 95.3%). The other document types used (4.7%) were mostly CPP or GMP compliance certificates from agencies in the United States, Australia, France, Sweden, and Germany.

The increased use of CEP may be due to its feasibility: API manufacturers can individually apply for a CEP by complying with the monographs of the European Pharmacopoeia. By contrast, quality certification appears to be more difficult to obtain when using other document types. For example, a CPP must be acquired from the final product manufacturer; therefore, receiving certification depends strongly on the status of the application, namely whether it is a new drug application (NDA) or abbreviated NDA (ANDA), in which the quality of both the APIs and final products should be evaluated by at least one country recognized by the Taiwan government (The designated countries include Australia, 2015). In some countries, a GMP-standard inspection may be mandatory before final product approval (CPG Sec. 490.100). Several criteria should be fulfilled before a CPP is issued.

Another potential factor leading to the predominance of CEP document may be that it simplifies the administrative requirements (Announcement no. 1011410816, 2012). First, the notarization of a CEP certificate has been exempted by the foreign affairs offices of Taiwan since December 2012. Second, the Taiwan Food and Drug Administration (FDA) accelerates the administrative process by requiring only a copy of the CEP rather than the original CEP because the current status of a CEP can be verified through the certification database on the EDQM official website (Certification: Search Database Online). CEP documentation facilitates verifying the suitability of an abbreviated application because it provides necessary information, such as the API name and manufacturing site. In summary, the status of a CEP document can be more openly validated than a CPP and GMP can be; in addition, the notarization of original documents remains an obligatory requirement for CPP and GMP applications (Announcement no. 1011410816, 2012).

Table 1
Assessment outcomes of reviewing time and acceptance rate.

Total applications			
732			
Full dossiers (174 ± 98 days)[a]		Abbreviated dossiers (73 ± 53 days)[a]	
517 (70.6%)[b]		215 (29.4%)[b]	
Acceptance	Rejection	Acceptance	Rejection
333 (64.4%)[b]	184 (35.6%)[b]	204 (94.9%)[b]	11 (5.1%)[b]

[a] Calendar days (mean ± standard deviation) spent in reviewing were presented.
[b] Number of applications in full and abbreviated dossier types (% in total applications) was presented as N (%).

3. Deficiencies leading to rejection of applications

Table 3 shows the deficiency distribution of rejected applications, categorized according to Common Technical Document sections and subsections (International conference on harmonization technical requirements, 2004). Some documents are exempted in abbreviated dossiers, including those of Process validation and/or evaluation (3.2.S.2.5), Manufacturing process development (3.2.S.2.6), Elucidation of structure and other characteristics (3.2.S.3.1), Validation of analytical procedures (3.2.S.4.3), Reference standards or materials (3.2.S.5), and Container closure systems (3.2.S.6) (Announcement no. 1001403285, 2011). Deficiencies in Specification (3.2.S.4.1) and Justification of specification (3.2.S.4.5) are intercorrelated; they are both presented in 3.2.S.4.1 to prevent duplication.

Deficiencies in full dossiers were distributed among the sections of Manufacture (3.2.S.2; n = 325, 37.7%), Control of drug substance (3.2.S.4; n = 203, 23.6%), and Stability (3.2.S.7; n = 131, 15.2%). In Section 3.2.S.2, the subsections of Control of materials (3.2.S.2.3) and Process validation and/or evaluation (3.2.S.2.5) were the main reasons for rejection. In Section 3.2.S.4, the subsections of Specification (3.2.S.4.1), Justification of specification (3.2.S.4.5), and Validation of analytical procedures (3.2.S.4.3) were the main reasons for rejection. Deficiencies in abbreviated dossiers were mainly distributed among the sections of Control of drug substance (3.2.S.4; n = 18, 47.4%), Manufacture (3.2.S.2; n = 13, 34.2%), and Stability (3.2.S.7; n = 6, 15.8%). For both dossier types, no deficiency was associated with General information (3.2.S.1).

Notably, both dossier types had some similarities. The top three deficiencies, namely Manufacture (3.2.S.2), Control of drug substance (3.2.S.4), and Stability (3.2.S.7), comprised more than 70% of all deficiencies in full (76.5%) and abbreviated (97.4%) dossier types. Furthermore, Control of materials (3.2.S.2.3) was the most prominent deficiency in the section for Manufacture (3.2.S.2) for both dossier types. These results can be compared with the mainstream observations of various organizations. In a study of a World Health Organization (WHO)-based API prequalification program (Ortega Diego et al., 2014), the most frequent deficiency section (3.2.S.2) and subsection (3.2.S.2.3) were consistent with this study in full but not abbreviated DMF applications. Similar conclusions were made in the EDQM certification program according to top deficiency rankings in the first assessment of new applications (Top ten deficiencies: new applications for Certification of Suitability (2011)). In the United States generic drug applications under the completeness assessment of type II DMFs (Zhang et al., 2014), the section for Manufacture (3.2.S.2) was ranked as having the highest