ACTIVE PHARMACEUTICAL INGREDIENTS (API) IN CHINA: APPROVAL PROCESS, TIMELINES, PRACTICE POINTS

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ABSTRACT Active pharmaceutical ingredient (API) application pathways in China have evolved substantially over the past 5 years. In 2018, the drug master file (DMF) system was introduced, superseding the previous approval procedure, which had been in place for more than ten years, and which was similar to that of finished drugs and therefore very costly and time-consuming for applicants. This paper reviews key application requirements and approval pathways for API in China, and explores challenges and key practice points for applicants.

KEYWORDS: China DMF, API, Registration practice points, China regulatory affairs.

INTRODUCTION

Active pharmaceutical ingredient (API) application pathways in China have evolved substantially over the past 5 years. In 2018, the drug master file (DMF) system was introduced, superseding the previous approval procedure, which had been in place for more than ten years, and which was similar to that of finished drugs and therefore very costly and time-consuming for applicants. See Figure 1 for a timeline of recent key regulatory changes.

This paper reviews key application requirements and approval pathways for API in China, and explores challenges and key practice points for applicants.

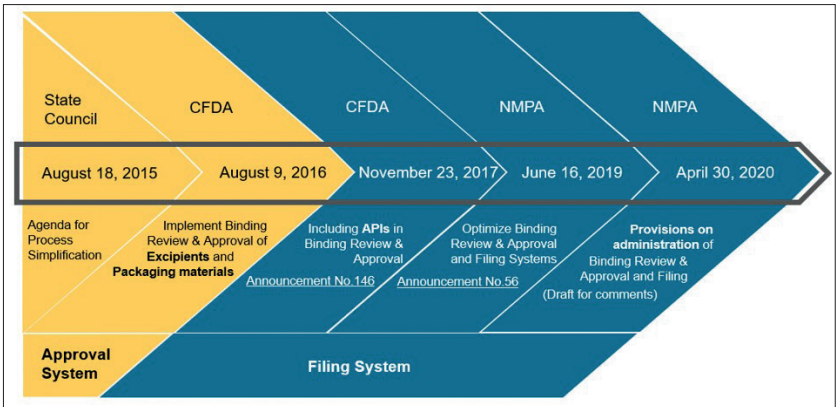

Figure 1 Timeline of the development of NMPA's DMF system.

Regulatory Framework

The SAMR (State Administration for Market Regulation) and NMPA (National Medical Products Administration) – former CFDA (China Food and Drug Administration) – are responsible for the management and registration of pharmaceutical products as well as medical devices, in-vitro diagnostics and cosmetics in China. The CDE (Center for Drug Evaluation) is NMPA's specific department responsible for the registration of pharmaceutical products.

China still has opportunities to improve alignment with other countries' more established pharmaceutical regulatory systems. However, with the introduction of the DMF system, China has taken a major step towards global pharmaceutical regulatory standards.

Although the DMF registration process in China is very similar to the procedure of the US Food and Drug Administration (FDA), it has its own peculiarities but on the whole the requirements for the review of DMF application dossiers in China continues the trend to become more in line with ICH (International Conference on Harmonization of Technical Requirements).

See Figure 2 for a summary comparison table of China, US and EU-types.

The DMF consists of confidential and detailed information on the production and quality control of APIs, excipients and packaging materials (together, "AEP"), which are submitted to NMPA and filed in their database. The data from the DMF will later be accessed by the NMPA as part of the approval of an end product, a drug.

Before DMF was introduced in China, API manufacturers could only send technical documents to individual customers (drugs manufacturers) to support the registration of drugs. Now, manufacturers can apply for their own DMF number to be used by many different drugs manufacturers in China. API manufacturers are no longer in the difficult position of needing to provide full production data directly to the drug manufacturer, as was the case under the old system.

Key steps & timelines

The process to obtain DMF in China for APIs (and other AEP) is now described.

First, a NMPA Legal Agent must be authorized. This legal representative must be a legal entity in China. Since the NMPA Legal Agent plays a crucial role in the application process, it should be chosen very carefully. The key selection criteria are: experience and expertise in China regulatory affairs, related product standards and the relevant authorities.

Then, the NMPA Legal Agent shall create an online account in NMPA's portal. After a successful application for a NMPA online account, the NMPA Legal Agent receives the username and password. All subsequent activities can be carried out or monitored through this account. Figure 3 shows the online platform with English translations of key items.

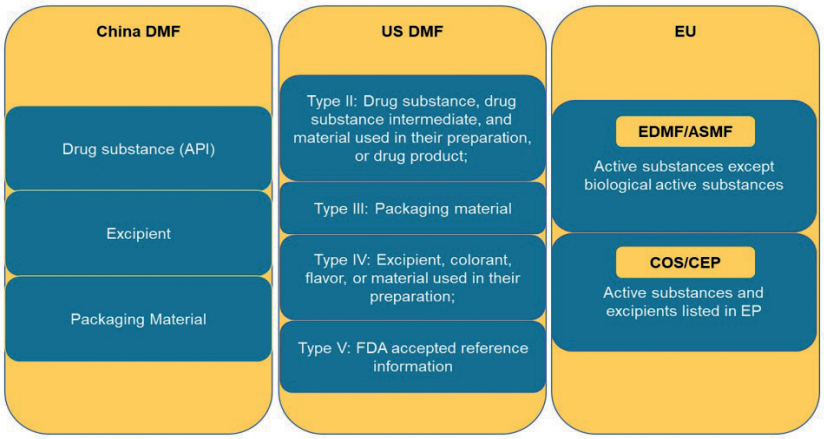

Figure 2. Comparison of China, US and EU drug master filing.

Figure 3 NMPA's online portal for drug master file

The application form for submission to NMPA is made via the online portal. All other application documents should be copied into one CD-ROM and then submitted to CDE per post. The DMF application documents for APIs are set out below. All documents must be submitted in Chinese.

- Module 1: Administrative documents and drug information
- Module 2: 2.3.S (ICH M4 CTD)
  2.3.S.1 Basic Information
  2.3.S.2 Production Information
  2.3.S.3 Characteristic Identification 2.3.S.4 Quality Control
  2.3.S.5 Reference substance
  2.3.S.6 Packaging system
  2.3.S.7 Stability
- Module 3: 3.2.S (ICH M4 CTD)
  3.2.S.1 Basic Information of the product
  3.2.S.2 Production Information of the production process
  3.2.S.3 Verification of characteristics
  3.2.S.4 Quality Control
  3.2.S.5 Reference substance
  3.2.S.6 Packaging material and system
  3.2.S.7 Stability

With a completed application form, the supplier will receive a pre-DMF number. Not all documents need to be submitted at this time. Therefore, the pre-DMF number can be obtained within 3 working days from submission. The supplier can already communicate this number to its customers, the drug manufacturers, and additionally issue an authorization (more formally, a Letter of Authorization or LoA). The supplier then may continue working on completing the documentation for the DMF and, in parallel, the drug manufacturers can begin obtaining drug approval with help of the DMF number.

The application documents must be prepared in accordance with Chinese regulation. The manufacturer's documentary evidence, such as business registration licence and authorization letter to the NMPA Legal Agent, must be notified by the manufacturer in the country of origin.

Submitted technical data will remain confidential with the NMPA. However, various information – including DMF number, product name, manufacturer name, manufacturing site address, import status, packaging specifications, product specification, update date and NMPA review status – will be made public in the NMPA filing platform at http://www.cde.org.cn/.

Acceptance of DMF Application - Status "I"

After submission, NMPA formally verifies that all required information has been received in a completeness review. Within two weeks, the status in the NMPA database will be set to "I". This status illustrates the progress of the technical review. "I" (inactive) indicates that the Completeness Assessment has been finished and that the application dossier is now ready to be reviewed by the evaluator, but that the technical review has not yet been completed with the drug. Refer to Figure 4 for a summary of the steps with timelines to status "I".

APIs (and other AEP) manufacturers can elect to undergo a bundle technical review together with the approval of the drug. This prevents unnecessary burden on the NMPA, improves the efficiency of the technical review and accelerates the process for the market approval of new drugs.

APIs (but not other AEP) can alternatively elect to undergo an independent technical review. On January 17, 2020, the NMPA introduced an official application fee of RMB 367,600.00 together with a new online application system for APIs. An official announcement with detailed payment instructions, such as price and payment target, was released on June 30, 2020 in Announcement No.75-2020.

An additional requirement for APIs (as compared with other AEP) is that they have to undergo registration tests in China.

Total timeline in the author's experience to status "I" for API is 9-10 months.

After the status in the NMPA database is set to "I", the testing process can begin. The test application is submitted to NIFDC (National Institutes for Food and Drug Control) following issue of the test notice. After NIFDC has reviewed (2 weeks minimum in our experience) the manufacturer should begin import of the test sample. Then the testing begins, which takes 5-6 months including review time. The test report is then transferred from NIFDC to NMPA.

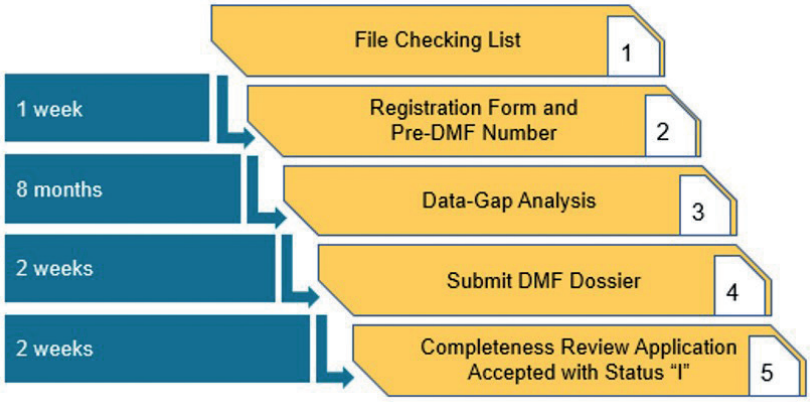

Figure 4. Timeline and key steps to status "I" for APIs in China.

Product Approval – Status "A"

During the approval of the drug, the NMPA evaluator is likely to issue a Supplementary Notice requesting additional information. The supplier must prepare the documents together with its NMPA Legal Agent and submit them to the NMPA.

If the DMF application satisfies all requirements, the status on the database is then set to "A" (Active). "A" indicates that the AEP is approved for use in finished drugs.

According to the announcement published in April 2018 (NMPA No. 2018-8), once the drug has been granted NMPA approval, the AEP can be imported into China without restrictions. In the past, among other requirements, an IDL (Imported Drug License) was required for the import and issuance of the "Imported Drug Customs Clearance Letter". The process of obtaining an IDL was comparable to that of a final drug.

Key challenges and practice points

APIs registrations have to be renewed every five years according to NMPA regulation (Packaging and Excipients do not need renewal). It is important to note that foreign manufacturers should submit their application at least six months prior to the expiration date and pay an application renewal fee of RMB 227,200.00.

However, the renewal portal and application requirements for APIs are still being finalised. It is expected to be finished in 2022 or 2023.

Any changes on the products or production process etc should be applied to NMPA for approval. Any changes on the basic information like company name and address etc should be filed to NMPA for record.

After receipt of the DMF number, suppliers of APIs (and other AEP) must submit an annual report (via their NMPA Legal Agent) to the NMPA so that their DMF is not suspended. The report consists of a summary of any changes (if applicable), quality management, and a list of drug manufacturers that have been authorized. Furthermore, suppliers have a legal obligation to drug manufacturers to report any changes or deficiencies in their AEP.

Certificate transfer problem

Since 2020, more and more foreign manufacturers have met different problems because of transferring the old certificate from the old system to the new DMF system.

A typical problem is that the same API can have two different DMF numbers in China, if the application for China approval was originally made prior to operation of the new system in 2018.

A typical example looks as follows: in 2016, a German API manufacturer applied for registration and was approved under the old system. Then in 2018, after the new system began operation, the German API manufacturer applied for the DMF registration under the new system because, at that time, new NMPA regulation for DMF had encouraged manufacturers to do so. The German API manufacturer received, for example, Number A.

In 2019, NMPA took action to transfer the old registration certificates from the old system to the new DMF system automatically. All manufacturers then received DMF numbers. In our example, the German API manufacturer will have then received Number B in respect of its 2016 approved API.

This resulted in the German API manufacturer holding two different DMF numbers, A and B, for the same product in China.

How to manage this problem?

1. Keep and use both DMF numbers: Then the Number B needs to be activated.
2. Keep both DMF numbers but use only the Number A: Then no action is needed.

We don't recommend to withdraw one number of A or B, since this could lead to potential problems in future because the online system may then show the number is no longer active.

An added complication is that the following problems are typical in relation to the automatic Number B transfer by NMPA in 2019:

- B is inactive: the status of B is "A", which should mean Active. But, in fact, it is not activated.
- B is empty: there is no document under B
- B has no legal agent, since there was no legal agent requirement under the old registration system of NMPA.

In all the above cases, submissions to NMPA will need to be made to correct the deficiencies.

ABOUT THE AUTHOR

Hamish King *is COO at Cisema, a China-focused CRO and regulatory consultancy founded in Munich and Beijing in 2002. A lawyer by training - admitted in Hong Kong and NSW, Australia - Hamish previously worked with UK "magic circle" firm Linklaters in Hong Kong, and has nearly 10 years' experience in the legal and regulatory fields. He has obtained the RAC and CFA qualifications. Regularly writing articles and speaking on China regulatory affairs and pathways for life sciences products, Hamish lives in Hong Kong.*