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# Regulatory Framework and Quality Considerations for Launching International Active Pharmaceutical Ingredients (APIs) into the China Market

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## Abstract

The pharmaceutical landscape in China is undergoing a significant transformation, driven by a growing demand for high-quality medications amidst improving living standards and an aging population. This surge in demand has attracted global Active Pharmaceutical Ingredient (API) manufacturers to explore opportunities within the China market. As China integrated into the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), the Chinese National Medical Products Administration (NMPA) implemented reforms to streamline pathways and enhance global collaboration.

To facilitate international API players in comprehending API regulations in China, this study delved into various regulations, announcements and guidance issued by the Chinese NMPA, combining insights gleaned from years of practical experience. This article presents a descriptive observational and review study on API regulations in China. It discusses the regulatory historical footprint of China Drug Master Files (China DMFs), the latest registration classification and quality considerations for APIs, focusing on starting materials, process validation, specifications and registration sample testing. Furthermore, it compares the registration classification to the US regulatory pathways. The study emphasizes the importance of regulatory compliance for international API manufacturers seeking to enter the Chinese market. Through this exploration, valuable insights are gained into the evolving regulatory landscape in China and its implications for international API manufacturers, aiding in their strategic decision-making processes and ensuring adherence to regulatory standards for successful market entry and product approval.

**Keywords:** Active pharmaceutical ingredient • Chinese national medical products administration • China drug master files • Registration classification • Regulatory pathways • Specifications • Registration sample testing

## Introduction

The API industry in China holds a pivotal position in the global pharmaceutical landscape. China manufactures and exports approximately 40% of the world's APIs due to their cost-efficient pricing. However, with the improvement in living standards and the increasing aging population in China, there has been a gradual surge in demand for high-quality pharmaceuticals in the Chinese market. This surge has attracted numerous international manufacturers of active pharmaceutical ingredients to explore opportunities within the Chinese market. Forecasts indicate that the Chinese API market is poised to experience a Compound Annual Growth Rate (CAGR) of 9.1% between 2024 and 2029 [1].

Since June 2017, when China officially became a member of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), there has been a concerted effort made by the Chinese National Medical Products Administration (NMPA), the central authority responsible for overseeing and regulating drugs, biologics, medical devices and cosmetics, to enhance global collaboration and harmonization in pharmaceutical regulations. Over recent years, the NMPA has undertaken significant reforms aimed at streamlining regulatory pathways, requirements and documentation by issuing numerous regulations and guidelines. In 2020, the China NMPA issued regulations such as the chemical drug registration classification and application information requirements and the drug registration management regulations, which clarify drug registration classifications, documentation requirements and regulatory pathways. Drawing from the regulatory concepts of the US drug master file system, the Chinese NMPA has established a framework to regulate APIs. Therefore, China API registration is also being referred to as China DMF in the API industry.

However, there are still significant differences between API regulations in China and the United States. This article aims to elucidate the regulatory framework and quality considerations essential for launching international APIs into the Chinese market. It focuses on specific regulatory pathways, the selection of starting materials, requirements for process validation, specifications and registration testing.

## Literature Review

- This is a descriptive observational and review study. Data which was relevant to API regulations was mainly gathered from their regulations and guidance issued by China NMPA and experience in practices which are below.

The studies based on China National Medical Products Administration, www.nmpa.gov.cn

Pharmacopoeia of the People's Republic of China, Edition 2020.

### The regulatory historical footprint of China DMFs

To align its drug regulatory pathways and standards with international norms and foster an environment conducive to pharmaceutical innovation, the NMPA issued a significant statement titled "Announcement on adjustments to the review and approval matters of active pharmaceutical ingredients,

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pharmaceutical excipients and pharmaceutical packaging materials" [2]. This statement introduced the concept of China DMF for the first time. According to the announcement, APIs used in non-innovative products could be registered in a DMF registration platform to be established by the NMPA and technical reviews would be triggered once associated finished product applications were submitted. This marked the inception of the China DMF system.

The NMPA subsequently issued the "Notice regarding further improvements to matters related to the review, approval and supervision of drug associations" [3]. This document aimed to address the issue of Active Pharmaceutical Ingredients (APIs) with existing marketing approval certificates during the transition period before the implementation of the Drug Master File (DMF) system. It allows APIs with marketing approval certificates expiring no earlier than November 27, 2017, to be automatically transferred to the platform, designated with an 'A' symbol, where 'A' symbolizes approved for marketing. Additionally, it introduces, for the first time, the possibility of applying for separate review and approval for both locally produced and imported APIs provided that this kind of API has already been used in domestically marketed formulations.

Meanwhile, the notice emphasized that the API DMF documentation and requirements should be in line with the guidance "Requirements for new registration classification application materials for chemical drugs" [4] issued by Center for Drug Evaluation of NMPA (CDE) in 2016. It's worth noting that even though the latest guidance only states that the applicant should prepare documentation according to ICH technical guidance, not mention that No.80 Guidance any more, in reality, the specific technical requirements in that guidance are still effective, applicable and usually required to comply with by the NMPA reviewers. Therefore, it's very important to understand the basic principles and requirements that will be illustrated in the following paragraphs and employ them in documentation. In 2020, the state administration for market regulation issued the drug registration management regulations [5] and NMPA issued a notice regarding requirements for registration classification and application dossiers of chemical drugs [6]. This registration classification also applies to APIs, with the application dossier required to comply with the ICH M4 CTD format.

Finally, in 2023, the NMPA issued the "Announcement on matters related to the re-registration management of chemical raw materials for pharmaceuticals" [7] officially outlining that the authority will issue marketing approval certificates, approved manufacturing process forms, specifications and labels to those who undergo successful evaluation by the NMPA. Domestic API manufacturers are required to apply for certificate renewal with the provincial authority six months before expiration, while international API holders should apply for certificate renewal with the NMPA six months before expiration. This announcement signifies that China's DMF system has essentially completed its establishment.

## Registration classification for chemical pharmaceutical products

As mentioned previously, in order to align with international norms and streamline the regulatory pathway, the NMPA issued an announcement titled "Requirements for registration classification and application dossiers of chemical drugs" [6]. This announcement primarily outlines five registration categories for chemical drugs, applicable to both APIs and finished products, as follows.

It's obvious that the China NMPA has learned from the pharmaceutical regulations of the United States and tailored its own drug registration classifications to fit the country's specific circumstances. For international API holders who plan to launch products into China market, understanding principles of registration classification and determination of registration classification is the first important thing before initiating the regulatory journey in China (Table 1).

## Regulatory pathways for API submission

There are two main pathways to get marketing authority for China DMF. The first one is request independent evaluation. The second one is bundle evaluation with finished products that use the particular API. According to regulations on drug registration management issued by NMPA on January 22, 2020, in the situation where a certain drug has been launched in China market and the applicant plan to launch the same kind of API that used in this certain drug, then the applicant is eligible to request independent evaluation and approval for the API. In this case, applicants do not need to link their APIs

**Table 1.** Registration classification for chemical products.

| Registration Classification | Definition | Compared to the US classification |
|---|---|---|
| Class 1 | Innovative drugs that have not been marketed in China or overseas. | Class I is similar to 505(b) (1), but it emphasized globally innovative, instead of not previously approved by China NMPA. It should not previously be approved by any countries authorities. |
| Class 2 | Class 2: Modified new drugs that have not been marketed in China and overseas. They refer to drugs that have their structure, dosage form, formulation and process, route of administration and indications optimized on the basis of known active ingredients and have significant clinical advantages. Therefore, Class 2 contains 4 sub-categories. | Class 2 products are similar to 505(b) (2). |
| Class 2.1 | Drugs containing enantiomers of known active ingredients obtained by isolating or synthetic methods, or esters of known active ingredients, or salts of known active ingredients, or modification of acid radicals, basic groups, or metal elements of known salted active ingredients, or formation of other non-covalent derivatives and possessing significant clinical advantages | 505(b) (2) |
| Class 2.2 | Drugs that contain known active ingredients with new dosage form (including new drug delivery system), new formulation process or new route of administration, and possess significant clinical advantages. | 505(b) (2) |
| Class 2.3 | New formulations that contain known active ingredients and have significant clinical advantages. | 505(b) (2) |
| Class 2.4 | Drugs with new indications containing known active ingredients. | 505(b) (2) |
| Class 3 | Drugs manufactured by domestic applicants imitating reference drugs marketed abroad but not yet marketed domestically. Such drugs should be consistent with the quality and efficacy of the reference products. | Similar to 505(j), only applicable for domestic applicants. |
| Class 4 | Drugs manufactured by domestic applicants imitating reference drugs that have already been marketed in China. Such drugs should be consistent with the quality and efficacy of reference products. | Similar to 505(j), only applicable for domestic applicants. |
| Class 5 | Drugs that have been marketed outside China. Class 5 contains 2 sub-categories. | 505(b) (1), 505(b) (2), 505(j), applicable for international applicants. |
| Class 5.1 | Innovative drugs and modified drugs that have been marketed outside China. | 505(b)(1) and 505(b)(2) |
| Class 5.2 | Generic drugs that have been marketed outside China. | 505(j) |

to any finished products to trigger technical review, which is totally different from the requirements of the US FDA. When it comes to bundle evaluation, it is similar to requirements of the US FDA. Letter of Authorization (LOA) is required from Market Authorization Holders (MAHs) of finished product. Only if the CDE received LOA, they initiate technical review of application dossiers. Innovative APIs and some generic API that has never been launched in China market must chose bundle evaluation. It's worth noting that some international MAHs of finished products only would like to export finished products to China market, without any plan to sell their APIs. In this case, applicants are allowed to include comprehensive API information as part of finished products application such as a part of ANDA and NDA. If the API is outsourced, the applicant can request API holder to submit API dossiers directly to CDE. Figure 1 and Figure 2 have shown independent review and bundled review of API submission respectively (Figures 1 and 2).

## Quality considerations

Quality is of paramount importance for APIs. NMPA reviewers rigorously evaluate it with utmost attention. As previously mentioned, the draft guideline "Requirements for new registration classification application materials for chemical drugs" [4] delineates specific requirements for API development and quality control that remain effective in practical application.

**Starting materials and process validation:** To avoid introducing uncontrollable factors into the quality of active pharmaceutical ingredients, the NMPA suggest that the chemical synthesis steps of active pharmaceutical ingredients from starting materials to final products be no fewer than three steps, excluding steps involving salt formation or esterification. In many cases where the API was manufactured by two steps, NMPA usually require the applicant to prolong synthesis steps in deficiency letter. Additionally, one China DMF only allow to contain one kind of manufacturing process. Lastly, process validation must be completed before submission, utilizing three consecutive commercial batches. When the applicant completes the process validation for a batch size, the NMPA approves the commercial production batch size accordingly. If the applicant plans to scale up batch size, a supplementary application must be submitted after the approval.

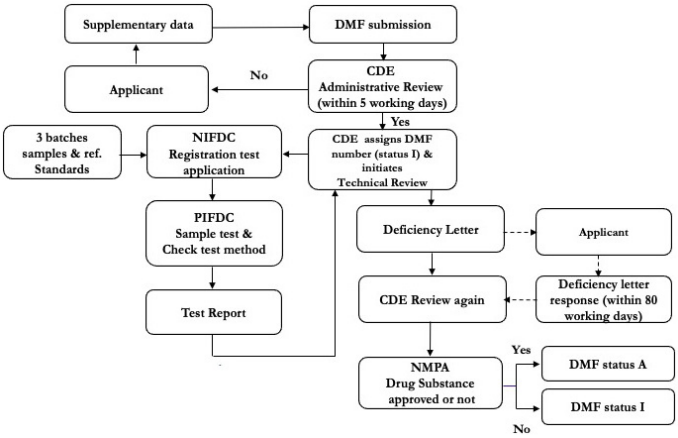


**Figure 1.** Independent review for API submission.

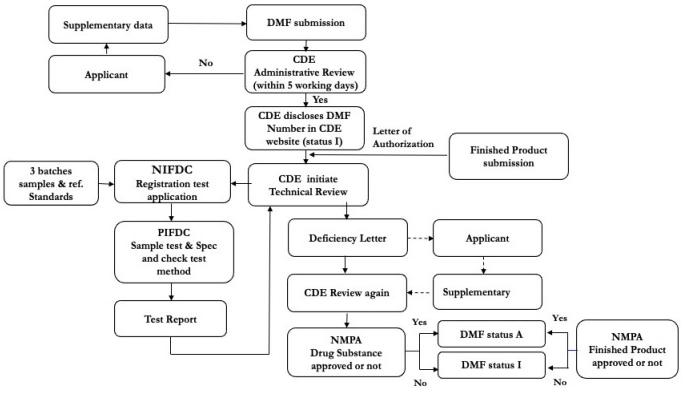


**Figure 2.** Bundled review for API submission.

**Specification and sample testing:** Specification is one of the most important factors impacting approval or not. The China NMPA enforces rigorous standards for APIs, requiring applicants to compare existing regulatory specifications listed in the United States Pharmacopeia (USP), European Pharmacopoeia (EP), Japanese Pharmacopoeia (JP) and Chinese Pharmacopoeia (ChP) and then draft the most stringent specification. The comparative studies are required to be presented in application dossiers. Additionally, as to physical-chemical test items, the NMPA encourage the applicants to use conventional method listed in Volume IV General Chapters of ChP, such as heavy metals and ignition Residue.

One major speed-limit step in obtaining approval for a product is registration sample testing. Every product, including APIs, drugs and biologics, must undergo this process before approval. Registration sample testing is a complex procedure, especially for international applicants, often resulting in detailed issues that lead to review suspensions and delayed approvals. The CDE issues a registration sample testing notice to the applicant within 5 working days of receiving the marketing application dossier. International applicants should apply for sample testing to National Institutes for Food and Drug Control (NIFDC), submitting samples, references, working standards and even analytical columns to NIFDC and Provincial Institutes for Food and Drug Control (PIFDC), respectively.

PIFDC validates the analytical procedures included in the application dossier and tests the samples to ensure the applicability of the analytical methods and that the samples comply with the proposed specifications. After completing sample testing, PIFDC submits testing reports and their opinions to NIFDC. NIFDC's experts evaluate the testing reports and opinions to formulate a final NIDFC report, subsequently submitting it to CDE and the applicant, respectively. Following this, CDE issues a deficiency letter to the applicant. Given the complexity and significance of sample testing, it's advisable for international API holders to gain an understanding of the ChP and regulatory landscape before developing specifications and analytical procedures and to prepare samples and necessary materials in advance.

# Conclusion

The API industry in China stands as a critical player in the global pharmaceutical industry, With the rising demand for high-quality pharmaceuticals in China, international API manufacturers are increasingly drawn to explore opportunities within this market. The regulatory landscape has undergone significant reforms since China became an official member of the ICH aimed at streamlining pathways and enhancing global collaboration in pharmaceutical regulation. The establishment of the China DMF system marked a significant milestone in aligning China's regulatory framework with international standards. Through various announcements and regulations, the NMPA has set forth clear guidelines and requirements for API registration, classification and approval processes. In particular, the intricate process of registration sample testing poses challenges for international applicants, often leading to delays in approvals.

As the Chinese pharmaceutical market continues to evolve, it is imperative for international API manufacturers to remain agile, adaptable and well-informed to capitalize on emerging opportunities and contribute to the advancement of global pharmaceutical innovation. By embracing regulatory harmonization and compliance, international API manufacturers can forge successful partnerships and achieve significant profitability within the Chinese API market.

# Acknowledgement

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## Conflict of Interest

There are no conflicts of interest by author.

## References


1. China Active Pharmaceutical Ingredients (API). "Market size and share analysis-industry research report - growth trends." (2024).
2. National Medical Products Administration (NMPA). "Announcement on adjustments to the review and approval matters of active pharmaceutical ingredients, pharmaceutical excipients and pharmaceutical packaging materials." (2017).
3. National Medical Products Administration (NMPA). "Notice regarding further improvements to matters related to the review, approval and supervision of drug associations." (2019).
4. Center for drug evaluation of NMPA. "Requirements for new registration classification application materials for chemical drugs." (2016).
5. State Administration for Market Regulation. "Drug registration management regulations." (2024).
6. National Medical Products Administration (NMPA). "NMPA issues requirements for registration classification and application dossiers of chemical drugs." (2024).
7. National Medical Products Administration (NMPA). "Announcement on matters related to the re-registration management of chemical raw materials for pharmaceuticals." (2023).


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