White Paper

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Electronic Submissions & eCTD Implementation in China

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How do you organize an electronic New Drug Application (NDA), Market Authorization Application (MAA) or biological product registration in China? In this article, we first shortly outline the regulatory reforms that preceded the current developments, then explain the function and general features of the (e)CTD and finally discuss the implications of the published eCTD guidelines on upcoming regulatory submissions.

Stepping up to **International Guidelines**

China has introduced a range of regulatory reforms for its pharmaceutical market in recent years. These reforms aim to facilitate access to China's drug market and to increase China's role in drug development, thereby addressing unmet medical needs.

One of the aspects of simplifying access to the Chinese pharmaceutical market has been adopting international standards, most notably by joining the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) in 2017. With this step, the Chinese regulatory authorities also accepted the Common Technical Document (CTD) format for regulatory submissions.

Furthermore, in September 2021, the guidelines for electronic submission of the CTD (eCTD) were published, which will come into effect on 29 December 2021.

Regulations for **China's Pharmaceutical Market**

In 2019, the Chinese National Medical Product Administration (NMPA) amended the Drug Administration Law (DAL), and in 2020 it introduced the Drug Registration Regulation (DRR). The DRR introduced the Market Authorization Holder (MAH) system, moving towards full lifecycle management of medicinal products on the Chinese market, including faster and improved Clinical Trial Application (CTA) procedures and requirements for post-market surveillance.

The MAH must be a Chinese pharmaceutical company or research institution responsible for the MAA with the corresponding data on pre-clinical and clinical studies, technical details, and the quality control system. The NMPA's Center for Drug Evaluation (CDE) is the institution that evaluates MAAs and subsequent documentation about medicinal products in China.

Since joining the ICH in 2017, the CDE has accepted submissions in CTD format. As of the end of 2021, eCTD submissions are possible for NDAs, chemical drug registrations and therapeutic and preventive biological product registrations. Other regulatory submissions, such as variations, are planned to be allowed in eCTD form in the future as well.

The **Common Technical Document (CTD)** and the **Electronic CTD (eCTD)** in China

The ICH developed the CTD as a model for dossier organization in 2001. It ensures the organization of required information about medicinal products in a standardized format and logical order. It also ensures that summaries of included information are provided in specified formats. In addition, the CTD allows regional differences in regulatory requirements to be covered in specific sections, thereby minimizing the adjustments that have to be made for submissions in different pharmaceutical markets. The CTD is required in the EU and accepted in the USA, Japan, and other regions.

The eCTD is the XML-based electronic format of the CTD and is basically a mechanism for drafting, maintaining, and delivering the CTD easily and securely. For most Competent Authorities (CAs), you can submit an eCTD application in several parts, also called sequences, which are numbered.

The CTD consists of four modules, numbered 2 to 4, Module 1 being the region-specific information, which is not formally part of the CTD. Module 3 contains the information on Quality, Module 4 on Non-clinical study reports and Module 5 on Clinical study reports. Module 2 comprises an overall summary of quality, overviews, and summaries of Modules 4 and 5. Further structuring is done by using Study Tagging File (STFs) specifications.

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For instance, the files for a pre-meeting for an Investigational New Drug Application would be an example of a first sequence. All submissions after that will be numbered accordingly.

To ensure compliance with ICH guidelines, eCTD software is usually used, and specific validator tools are available to check the completeness and accuracy of the data to be submitted. The current version of the eCTD is version 3.2.2, but version 4.0 has been developed and is already in pilot use in some regions and will be fully implemented in most regions by the end of 2023.

eCTD Guidelines in China

The CDE has required Clinical Trial Applications (CTAs), chemical drug registrations and therapeutic biological product registrations in CTD format since 2018. However, the guidelines for electronic CTD submissions of 29 September 2021 are currently only for NDAs and Biological License Applications (BLAs) for chemical drugs and therapeutic and preventive biological products. In addition, they concern category 1 products, which are innovative drugs that have not been marketed in China or overseas, and category 5.1, drugs marketed overseas but not in China.

The guidelines follow the ICH 3.2.2 specifications for eCTDs, meaning that Module 2 to 5 will adhere to the CTD format. Making the application in electronic format is optional. However, when the eCTD format is chosen, a paper copy of the CTD still needs to be handed in at the latest 5 days after electronic submission. You must also include a declaration of consistency between the electronic and paper formats. The eCTD should be delivered on CD or DVD, and in the future an online portal is intended to be developed. The first sequence should be numbered 0000 for the CDE instead of 0001 for the FDA. The primary language of all documents should be Chinese (Mandarin), but references to English-language documents are permitted. Validation of submissions will be free of charge and can be done through a web link on the CDE website, and will also be in Chinese. Currently, validation only requires information about errors and warnings, not prompt information, but the future expansion of validation features is planned.

The NMPA also lists more detailed specifications, validation criteria and submission requirements on its website.

The guidelines include, for example:

- requirements for descriptions of Key Starting Materials (KSMs) and their quality checks;
- compliance checks of vendors and other partners;
- biological activity study specifications;
- manufacturing process;
- quality and compliance details for all manufacturing processes (including GMP and ISO certificates).

Considerations for **Regulatory Submissions in China**

Suppose you register a drug or biological product on the Chinese pharmaceutical market. In that case, you have to be familiar with the guidelines and regulations of the NMPA and the CDE.

The Drug Registration Regulation requires a Chinese pharmaceutical company as a MAH, meaning non-Chinese companies need a Chinese partner. First of all, this is useful because regulatory submissions to the CDE have to be in Chinese. In case you plan to market a medicinal product already approved in other regions, in the simplest case, this would mean translating the regulatory documentation and ensuring you meet any additional requirements.

However, one of the reasons China is harmonizing its regulation for medicinal products with international standards is to accelerate drug approval and to stimulate drug development in China. Therefore, it is recommendable to find a local partner with experience with clinical development and regulatory affairs, including clinical study planning and performance, medical and CMC writing, translating to Chinese, reviewing and validating regulatory documents, and submitting CTAs and NDAs to the CDE.

By including a Chinese partner early on in drug development and marketing application processes, you can accelerate the regulatory process by ensuring writing, formatting, review, validation and submission processes run simultaneously when possible, also in multiple regions. As a result, you can accomplish faster drug approval in China and an earlier revenue generation.