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White Paper

Chinese Excipient Regulation – a Globally Unique Challenge

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China: A Promising Yet Challenging Pharmaceutical Market

With a population of 1.4 billion and an aging society, China is a highly attractive market for pharmaceutical companies. The most populous country in the world is expected to become the second biggest pharmaceutical market worldwide after the USA as early as 2020.

However, the outstanding market opportunities are accompanied by substantial challenges for companies who want to manufacture, import or sell drugs in China. The regulatory structure and requirements are complex – and are currently undergoing major changes in the wake of several reforms. Most importantly, regulatory compliance is required not only for the active pharmaceutical ingredient (API), but also for excipients used in drug manufacturing. In fact, it is mandatory to register all excipients used in drugs sold on the China market, including those used in imported drugs – a globally unique situation.

The recent reforms have already increased regulatory efficiency and transparency and have to some extent also resulted in a better alignment with international standards. In August 2019, the China Drug Administration Law was revised, with changes that will go into effect on December 1st, 2019. This law aims at enhancing drug safety and improving public health. It includes most of the previous reform outcomes such as the China Marketing Authorization Holder system, and the co-review regulation relevant for APIs, excipients and packaging alike. Nevertheless, keeping pace with the constantly evolving regulatory requirements remains an enormous challenge, and efficiently planning and implementing all necessary steps is a major undertaking.

This white paper presents an overview of the Chinese excipient regulation and the most relevant changes for both drug and excipient manufacturers. It provides specific information regarding the unique excipient registration process, based on long-standing expertise in regulatory affairs and experience with Chinese authorities and business practices.

In a nutshell, the white paper's goal is to help readers find an efficient approach to regulatory compliance and, ultimately, to manufacturing and marketing pharmaceutical products on the Chinese market.

The Evolution of Excipient Regulation in China

The pharmaceutical regulatory environment in China has always been perceived as highly complex. Hence it can be helpful to review the most important milestones in the evolution of excipient regulation, as well as the structure of the respective authorities.

Mandatory registration of excipients becomes common practice:

Excipients came into regulatory focus in 2001 when article 11 of the Pharmaceutical Administration Law stipulated that excipients used for pharmaceutical production should meet the requirements for medicinal use. This very general wording led to quite inconsistent approaches. For instance, some Chinese provinces regulated excipients as APIs, while others did not regulate them at all. In 2005, the China Food and Drug Administration (CFDA) issued the Pharma Excipient

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Dossier Requirements for industry, proposing excipient registration according to the same process as APIs and stand-alone reviewed by the Centre of Drug Evaluation (CDE) for import and novel excipients, and by the local FDA for excipients described in the Chinese Pharmacopeia (ChP).

Roughly ten years after issuing this regulation, the Chinese State Council initiated substantial reforms for drug approval processes in general, and the first to introduce co-review for excipient and packaging materials (2015, Notice No. 44). The reforms were prompted by a substantial backlog in drug review. China's pharmaceutical industry had developed rapidly in the interim, resulting in a broad range of new, improved medical products. However, the approval process couldn't keep pace with these rapid innovations and had to be supplemented and improved on numerous occasions, seriously limiting its efficiency. Hence the reform aimed at establishing a more transparent and more efficient process for drug approval and, as a result, also for excipient approval.

Change from stand-alone review to bundling review (2016 No. 134, CFDA):

These efforts resulted in the CFDA issuing a new regulation in 2016. Apart from increasing the number of reviewers from the previous 100 to ca. 800 in 2019, the 2016 regulation replaced the previous stand-alone review scheme for excipients with "bundling review." In the first step, pharmaceutical companies submitted their dossiers and received a drug application number, which they forwarded to the manufacturers of the excipients included in their product. In the second step, the excipient manufacturers submitted their dossiers with the same drug application number. The reviewers could now process drug and excipient applications together, identifying the "bundles" by their shared drug application number.

Change from bundling review to co-review (2017 No. 146, CFDA):

Not long after, in November 2017, the bundling review was replaced by the "co-review," or joint review, approach. Now the excipient manufacturer (and no longer the drug manufacturer) is the first party to submit an application. After receiving a registration number, they issue a letter of authorization (LOA) to the pharmaceutical manufacturer who uses the respective excipient. The latter then includes the LOA in its dossier when applying for marketing authorization for drugs on the Chinese market.

Amendments to co-review: ChP classification as the basis for dossier requirements (2019 No. 56, CFDA):

In 2018, the classification of excipients as listed in the Chinese Pharmacopeia (ChP) was introduced (1). Since then, this classification has served as the basis for the dossier requirements for excipients. The revised dossier requirements were published in a recent announcement from July 2019. The amendments also include changes to the exemption list.

In addition to these developments, the Chinese regulatory authorities also engaged in an intensive exchange with the U.S. Food and Drug Administration (FDA), the respective EU authorities and the European Directorate for the Quality of Medicines & HealthCare (EDQM). Moreover, China has been a member of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) since 2017. The implementation of the ICH guidelines in China is an ongoing process.

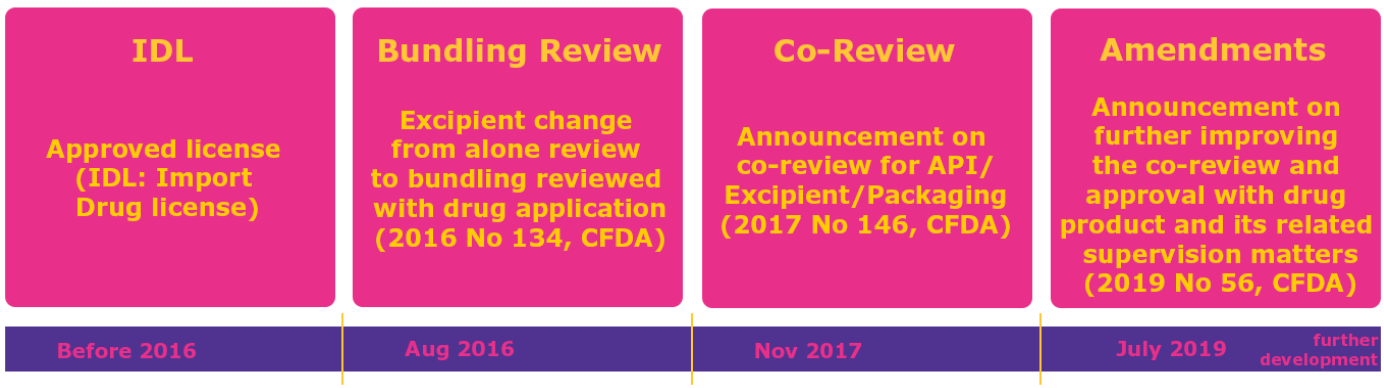

Table 1:
Milestones in the Evolution of Excipient Regulation in China

NMPA (formerly CFDA)	**National Medical Products Administration** (NMPA) (formerly the China Food and Drug Administration, or CFDA): primary regulator for drugs, medical devices and cosmetics. (2)
CDE	**Center of Drug Evaluation:** as part of the NMPA, the CDE is responsible for the technical review of registration dossiers, while also providing regulations and guidance on the evaluation and approval of drugs, including excipients and APIs.
CFDI	**Center for Food and Drug Inspection:** also part of the NMPA, responsible for formulating and revising the rules and technical documents on the inspection of drugs, medical devices and cosmetics.
NIFDC	**National Institutes for Food and Drug Control:** oversee the quality control for pharmaceutical products and medical devices.

Table 2:
Overview of the Main Pharmaceutical Regulatory Authorities in China

Registration Process for Excipients in China Based on 2017, No. 146, CFDA

Given the numerous revisions of the relevant guidelines, they are difficult for drug and excipient manufacturers to understand in detail. What steps do they have to take to ensure regulatory compliance in China? What requirements must be met regarding the application dossier?

Filing the excipient dossier

As of December 2017, according to CFDA announcement No. 146, all pharmaceutical excipient manufacturers or owners, domestic or foreign, must submit their dossiers to the CDE. After a successful completeness check, a registration number is created on the CDE registration platform. Then the registrant can issue a LOA to its customer (i.e., the drug manufacturer) for their respective drug application. In fact, the drug manufacturer or owner can only submit an application if it provides valid registration numbers for all excipients used. If certain excipients have already been successfully registered in the context of previous drug reviews and have maintained their registration number, there is no need for a new review.

Getting approval – "A" status

After successful submission by the drug manufacturer, the CDE commences the assessment process. The applicant must answer any questions regarding the product and is informed if there is a deficiency letter for the API, excipient or packaging material. If so, the CDE contacts the respective excipient registration owner. Once this assessment has been finalized, the drug approval is issued to the drug manufacturer. At the same time, the status of the co-reviewed excipients is changed to "A" for "Active" on the CDE platform.

Maintaining the "A" status

Pharmaceutical excipient manufacturers must submit annual product quality management reports to the CDE - in the first quarter of each year - in order to keep their DMF registration number active. Important quality-relevant changes to the excipients must be communicated to the drug manufacturer as well, who will assess their impact on the final drug product.

However, as long as drug manufactures continue to use an excipient on the CDE registration platform and the LOA from the excipient manufacturer, their drug application will be accepted. If the status of the excipient in question has been maintained, the NMPA can use the excipient registration data directly; however, another technical review may be necessary if the CDE decides that the use of the excipient has changed.

This highly formalized co-review process requires a firm command of the Chinese language and familiarity with Chinese business practices. It is therefore highly recommended to work with an agent in China, as the relevant dossiers and the registration platform are only available in Chinese. In addition, close cooperation and clear communications between the excipient manufacturer, drug applicant and CDE are essential to fostering an efficient process.

Chinese Dossier Requirements for Excipients

Just like the individual process steps, the content of the dossier must fulfill very specific requirements. General information on the company and the excipient itself, such as its name, structure, characteristics, approval and usage information, has to be included in the registration dossier. Moreover, detailed information on the manufacturing process is required, together with a list of equipment and process validation data. Lastly, the dossier must include quality control specifications with descriptions of the analytical methods and validation.

The level of detail required for the registration dossier is based on the excipient classification as revised by the NMPA in July 2019. Excipients are classified into products with or without a history of use in approved drugs. The latter comprises completely new molecules, as well as molecules with simple changes to their structure or a changed route of administration. Products with a history of use are in turn divided into two groups of excipients: the first group comprises those excipients that are included in the ChP or the pharmacopoeias of the European Union (Ph.Eur.), the United States (USP), Great Britain (BP) or Japan (JP). The second group comprises those that are not included in these documents. And finally, there are excipients used in foods or cosmetics.

As confirmed in announcement No. 56, which went into effect on August 15, 2019, the NMPA has also identified low-risk excipients that are exempted from mandatory registration and issued an updated exemption list (see Table 3). Among these exemptions are corrigents, like sweetening agents, flavors, colorants, pH adjusters and inorganic salts. However, the final decision on whether or not a certain excipient needs to be registered must be confirmed by the CDE and depends on how said excipient is used in a given drug formulation.

NMPA Interpretation issued in July 2019 (NMPA announcement 2019 No. 56 - Appendix 3)

3 Pigments (Colorants), Inks
- Iron oxide, plant carbon black, Cochineal
- Benzen free inks

(for capsule inscription)

2 Flavors, Spices

Orange flavor, banana flavor, Vanillin
- Follow GB National Food Safety Standards, if listed in there

4 pH adjusters
- Several inorganic acids
- Some organic acids

Injectable applications included

exemption list for low risk excipient

1 Corrigents

(sweeting agents)
- Sucrose, glucose, ...
- Mannitol, sorbitol, ...
- Saccharin Na, Sucralose, etc.

5 Inorganic salts
- "With simple preparation technology and stable physicochemical properties"
- Injectable appl. included

Note: The final exemption of registration of an excipient need to be confirmed by CDE depends on how excipient is used in drug formulation.

Table 3:
Exemptions for Low-risk Excipients

Legal Basis for Mandatory Compliance with the Chinese Pharmacopeia

Most excipients must be registered and are submitted for regulatory approval in China. All excipients used in drugs for the Chinese market must be compliant with the ChP, as stipulated in the Chinese Pharmaceutical Administration Law issued in 2019. Article 28 explicitly requires drug production to comply with the National Drug Standard, which combines drug registration standards issued by the ChP committee, those approved by the CDE, and others released by the NMPA (3).

The first ChP was published in 1953. Since 1985, the ChP committee has released an updated version every five years. Since 2005, an English version has also been available. At that time, the registered IDL standard was accepted. In 2015, the ChP committee declared that all drugs marketed in China must comply with the ChP. A further statement released in 2016 underscored that imported drugs and their components must also comply with the ChP.

The current ChP edition includes 270 excipient monographs. In 2019, the ChP committee issued the "National Excipient Standard Drafting Work Best Practice" for public comment, encouraging the industry to actively participate in the ongoing excipient monograph revision. The goal for the 2020 edition is to add another 100 excipient monographs and to promote the harmonization with other national pharmacopeias in the European Union, the United States and Japan.

Seizing the Opportunities Presented by the Chinese Pharmaceutical Market

The reforms made over the past several years have led to a much more efficient and transparent excipient registration process. In addition, the recent regulations have harmonized the registration procedure with international standards to some extent. Although excipient registration is still only mandatory in China, the procedure is quite similar to the US DMF system, which all global pharmaceutical companies are familiar with. Now both domestic and foreign companies are subject to the same registration requirements. And, most importantly, all companies have an equal opportunity to tap the potential of the Chinese pharmaceutical market.

However, some challenges remain: the co-review regulation in force since the end of 2017 includes highly detailed dossier requirements, comparable with those for APIs. As there was no transition time, many excipient manufacturers now lack the technical dossiers they need for successful registration. As a result, many drug manufacturers cannot yet register their products in China. In addition, the need to disclose manufacturing and quality control details has triggered some heated discussions concerning property rights. Finally, the ChP has not yet been fully harmonized with other international compendia, which forces global pharmaceutical companies to perform additional comparisons of methods and cross-validation checks. Nevertheless, the fast-growing Chinese pharmaceutical market is highly attractive and holds tremendous potential. Overcoming the remaining challenges is both rewarding and feasible. The Chinese market is now poised to become even more open, which will further increase its potential value for pharmaceutical companies. Readers who want to know more about the Chinese excipient regulation and how to deal with it can visit our webinar here:

www.emdmillipore.com/china-excipients-regulation

Glossary (in alphabetical order)

API	**Active Pharmaceutical Ingredient:** is the part of any drug that produces its effects.
CDE	**Center of Drug Evaluation:** as part of the NMPA, the CDE is responsible for the technical review of the registration dossiers.
CFDI	**Center for Food and Drug Inspection:** as part of the NMPA, responsible for formulating and revising the rules and technical documents on the inspection of drugs, medical devices and cosmetics.
ChP	**Chinese Pharmacopeia:** Chinese reference work for pharmaceutical drug specifications, containing directions for the identification of compound medicines. Descriptions of preparations are called monographs.
DMF	**Drug Master File or DMF:** a document prepared by a pharmaceutical manufacturer and submitted solely at its discretion to the appropriate regulatory authority in the intended drug market. It provides the regulatory authority with confidential, detailed information on the facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of human drugs.
ICH	**International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use:** is an initiative that brings together regulatory authorities and the pharmaceutical industry to discuss scientific and technical aspects of pharmaceutical product development and registration.
IDL	**Import Drug License:** drugs already marketed in another country need to apply for an IDL to be approved for import into China.
IPEC	**International Pharmaceutical Excipients Council:** a global organization that promotes the quality and safety of pharmaceutical excipients.
NIFDC	**National Institutes for Food and Drug Control:** is tasked with the quality control of pharmaceutical products and medical devices.
NMPA (formerly CFDA)	**National Medical Products Administration (NMPA) (formerly the China Food and Drug** Administration, or CFDA): the primary regulator of drugs, medical devices and cosmetics in China.

References

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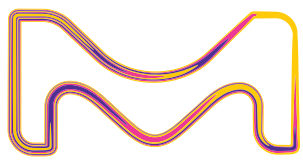
3. Zhang, Wei, 2018: Chinese Pharmacopoeia (ChP) and Progress in the Compilation of ChP 2020. ChP-EDQM Workshop on Pharmaceutical Excipients. Strasbourg, France, September 18, 2018. https://www.edqm.eu/sites/default/files/presentation-workshop_excipients-chinese_pharmacopoeia_and_chp_2020-september2018-zhang_wei.pdf, accessed August 19, 2019.



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