TOPRA Webinar

Comparison of China DMF with EU and US

Q&A

Thank you for participating in our webinar co-organised with TOPRA. This webinar is about China Drug Master Filing (DMF) versus EU and U.S DMF. Accestra will provide an overview of the DMF registration systems covering Active Pharmaceutical ingredients (APIs), Excipients & Packaging Materials. Thanks to global harmonization efforts, the Chinese DMF regulatory system is becoming more similar with US DMF, EU ASMF, CEP and Japanese DMF requirements. However, local regulations and differences still exists and it is essential to understand these to minimize risks and issues further down the line with DMF submissions to China CDE & NMPA.

If any additional questions, please contact us: **info@accestra.com**

Please find the Q&A below:

Q1: If have integral DDC product with lots of device (packaging) info in Modules 3.2.P.2.4 & P.7 can you simply x-ref to these sections for safety, testing/CoA's, stability etc.

A1: Considering the definition of DDC product in China could be different with other countries, it is crucial to clarify the classification of DDC products in China first. According to current technical guideline for DDC registration, if the DDC is classified as a device-based product, DMF filing is not required for the packaging of the product, while if the DDC is classified as a drug-based product, DMF filing is applicable for packaging.

Additionally, it is also recommended that applicants determine whether the device/packaging combined in the DDC product is classified as a packaging product in China. We have encountered many cases where the classifications of a product differ between its country of origin and China.

If the device/packaging is indeed classified as a packaging product, when applying for DMF registration, applicants can refer to the data in Modules 3.2.P.2.4 and P.7 for sections related to safety, testing/CoA's, and stability data. However, we strongly

advise conducting a data completeness analysis as the data in Modules 3.2.P.2.4 and P.7 may not fully comply with DMF requirements in China.

On the other hand, if the device/packaging is classified as a medical device, the applicant should consider applying for medical device registration, or register the whole DDC product following the DDC registration guideline, which involves a classification determination procedure.

For further information, please do not hesitate to contact us and provide your specific situation.

Q2: If there is a manufacturing process for API with an intermediate manufactured at two different manufacturing sites but the final API is only manufactured at one site, can this be covered by one DMF in China?

A2: The background information provided is insufficient to give an accurate answer to this question. To determine whether an API with an intermediate manufactured at two different sites can be registered under one DMF, more specific information is needed. We suggest contacting the Accestra team for a detailed discussion.

Q3: Packaging - means ONLY the primary packaging?

A3: According to the “Chinese Provisions of Drug Registration” and the "Announcement on further improving the associated review and approval with drug product and its related supervision matters" (Decree No. 56, 2019) published by NMPA, DMF filing for packaging materials is usually only required for primary packaging materials. However, for finished drugs that require additional functional secondary packaging materials (such as high barrier property outer bags), or for drugs that are sterilized after being packed with both primary and secondary packaging materials, the primary and secondary packaging materials should be considered as a packaging system, and the materials of the secondary packaging materials should also be provided.

Q4: Could you please confirm if Chinese Health Authority issues an approval letter

once they approve a DMF for an Active Pharmaceutical Ingredient? thank you

A4: After successfully passing the technical review and final approval process, NMPA will issue a digital "Notice of Approval" to the API product applicant. Along with this notice, other relevant documents such as the approved specification, label, and manufacturing process information, which have been verified by NMPA, will also be attached.

Q5: For a packaging DMF, similar to a US Type III DMF (for a MDI/DPI), can you have 1 DMF if the products detailed in it are the same type, but are destined for different pharma customers? Also, if the materials used are not always the same (different elastomer type, for example), can they also go into 1 DMF?

A5: As per the regulation of Decree No. 56 (2019), products sharing the same production process, materials, and function may be registered under a single DMF. Therefore, if your products vary only in their shape or size design for different pharmaceutical customers, but have the same material, production process, and intended use, they can be registered as a single DMF. Similarly, if it is a packaging system, all the detailed materials of each packaging component can be included in a single DMF. However, if the materials of different product types differ, they should be registered in separate DMFs. For instance, bromobutyl rubber stopper and chlorobutyl rubber stopper should be registered as two DMFs.

Your product may have many different type numbers, which could make it complicated to determine the required DMF numbers. To assess your specific needs, we recommend contacting the Accestra team to evaluate how many DMF numbers are necessary for your product.

Q6: Do you have any experience about a GMP on-site inspection triggered by the DMF filing to the CDE? thank you

A6: DMF registration usually will not directly trigger on-site inspections for overseas produced AEPs.

According to “Regulations on the Administration of overseas Inspection of drugs and medical devices（No.101,2018）”, Article 8 : NMPA shall determine inspection

tasks through risk assessment and random inspection according to the proposals of relevant departments for products to be inspected and its research and production sites. When necessary, it may carry out extended inspection on production sites, suppliers or other contract agencies of APIs, Excipients and packaging materials (AEPs).

Therefore, on-site inspection for AEP DMF is not mandatary, it's risk assessment or for-cause based when NMPA inspect finished drugs.

DMF registration for overseas-produced AEPs usually does not directly trigger on-site inspections. But after the binding review with the drug product, an extended on-site inspection on AEP products may be triggered based on the risk level of the drug product.

According to the "Regulations on the Administration of Overseas Inspection of Drugs and Medical Devices" (No.101, 2018), NMPA determines inspection tasks for products and their research and production sites through risk assessment and random inspection based on proposals from relevant departments. If necessary, it may carry out extended inspections on production sites, suppliers, or other contract suppliers of APIs, excipients, and packaging materials (AEPs). Therefore, on-site inspection for AEP DMFs is not mandatory for all applications; instead, it is based on risk assessment or for-cause inspection when NMPA inspects finished drugs.

Q7: In reality for conventional global pharmacopoeial excipient how much detail is required?

A7: According to the regulations of AEP associated review (draft for public comments) released in 2020, for excipients that have been used in food and drugs for a long time and whose safety has been recognized (such as non-high-risk excipients included in USP, EP, JP, BP & ChP) with usage, dosage, and function within the scope of routine use, data requirements can be simplified. The applicant can decide whether to apply for DMF for this product.

In this case, the finished drug applicants can include excipient information in the application materials for the drugs, and CDE may require supplementary technical data during the technical evaluation as necessary.

CDE will publish and update a list of such products. In case of any uncertainty, we

suggest the applicant provide the product name to the Accestra team to confirm its eligibility.

Q8: Does a packaging material DMF require the 5 year renewal?

A8: Renewal is not required for a packaging material DMF, and there is also no approval notice issued for packaging materials. Once approved, the status of the DMF number in the CDE platform will change from "I" (inactive) to "A" (active).

Q9: not directly related but do you have any info on status of China application to be PICS GMP member?

A9: NMPA has applied and launched the pre-accession program at PIC/S since September 2021, and currently NMPA is still actively promoting the work.

Q10: Can any types of biological products be submitted in a DMF (biological active substances or excipients)?

A10: The current China DMF policy applies only to chemical APIs, meaning that DMF registration is not typically applicable to APIs for biological products. However, for certain products, the classification may differ in China compared to other countries. Therefore, it is strongly recommended that applicants provide specific product information to the Accestra team for confirmation. For instance, heparin derived products are classified as chemical APIs in China, while they may be classified as biological APIs in other countries.

For biological product origin excipients, they can be registered in a DMF according to Decree No. 56 (2019).

Q11: Can you have more than 1 local agent (for different DMFs)?

A11: Yes, for different DMFs, you can have more than 1 local agent.

Q12: What stability data is needed for packaging DMFs.

A12: In China, stability data is usually required for packaging materials made of polymers such as plastics and rubber products. The stability study should include accelerated stability data and long-term stability data for at least one batch of representative samples. If you need more information on how to design the stability study for packaging materials, please contact the Accestra team for assistance.

Q13: Is compliance with Chinese Pharmacopoeia mandatory or could Ph Eur or USP be accepted?

A13: In general, products are required to comply with the standards set by the Chinese Pharmacopoeia (ChP). Therefore, when an applicant sets the product specification, they should also consider ChP and conduct a thorough comparison study with the European Pharmacopoeia (EP), United States Pharmacopeia (USP), or Japanese Pharmacopoeia (JP). However, in some cases, meeting both EP/USP and ChP simultaneously can be difficult, particularly for certain test items or special requirements from drug manufacturers. In such situations, it is essential to provide detailed information for further evaluation.

Q14: For DMF Annual Reports, is the content similar to US DMF Annual Reports (i.e. only administrative information e.g. changes to list of companies authorized to refer to DMF,) or does it also include CMC updates?

A14: The Chinese DMF annual report is similar to that of the US, and a CMC update is not required. Currently, the NMPA has only issued a general requirement for the AEP annual report in 2019, with few details provided. For example, the annual report should include a summary of product changes in the last year, as well as information on drug companies authorized to refer to the DMF. Accestra team can provide a template and prepare the annual report for applicants.

Q15: Are annual reports required for packaging DMFs?

A15: Yes, it is required.

Q16: Is China pharmacopoeia aligned with EP?

A16: China pharmacopoeia is not aligned with EP. There are still many differences.

Q17: Could you please confirm if it would be acceptable by CDE that the API manufacturer outsources to a Chinese lab the validation of the microbiological purity and bacterial endotoxin tests (following the requirements regarding the strains and source of strains set in Chinese Pharmacopoeia) , but once the method is validated then carry out routine testing according Eur. Ph. by the API manufacturer ?

A17: CDE accepts the Chinese lab validation data. If the test method follows the requirements regarding the strains and source of strains set in Chinese Pharmacopoeia, this test method should be transferred to applicant's lab for release test. However, if the Chinese lab proves the strains used in the Chinese pharmacopoeia method are equivalent to the trains used in the EP pharmacopoeia (ATCC method is equivalent to CMCC method for example), the EP method can still be used to routine testing.

The Center for Drug Evaluation (CDE) accepts Chinese laboratory validation data. If the test method follows the requirements regarding the strains and sources of strains set in the Chinese Pharmacopoeia, it should be transferred to the applicant's laboratory for routine testing. However, if the Chinese laboratory proves that the strains used in the Chinese Pharmacopoeia method are equivalent to the strains used in the European Pharmacopoeia (for example, the ATCC method is equivalent to the CMCC method), the European Pharmacopoeia method can be used for routine testing.

This is a typical question for many imported APIs. The answer here is only for a reference and many details need to be considered. Please do not hesitate to contact us for a further discussion to make sure the work is comprehensive.

This is a common question for many imported APIs. The answer provided here is intended as a reference, but there are still many details that must be taken into consideration. We encourage you to contact us for further discussion to ensure that proposed work is comprehensive and meets your specific needs.

Q18: Can the drug product manufacturer submit their application to reference an API DMF even if it is under active review or only after receiving approval notice?

A18: An active or inactive API DMF can both be referenced for an associated drug product registration, as long as it is published on the CDE DMF platform.

Q19: If no annual report legislation & no change then it can be omitted

A19: According to Decree No. 56 (2019), an annual report should be submitted for the AEP and drug product, regardless of whether any changes have occurred or not.

Q20: For API DMF, can I submit the closed part via one Chinese agent no1. and the open part of the API DMF with the drug product module via a second Chinese agent. For IND (PK study)

A20: In China, all API DMF data are considered confidential, and there is no concept of an open or closed part. For an IND application, a DMF can be directly registered with a Chinese local agent for the drug product to reference. Alternatively, the materials can be provided directly to the CDE through an appointed Chinese local agent without disclosing the information to the drug applicant, as DMF is not mandatory for API in the IND stage. Accestra team has extensive experience in dealing with this scenario.

Q21: what is current regulation to change the API supplier to EU

A21: We will provide a general answer to the question of how to change the API supplier to China since the topic of this webinar is about China DMF.

To change the API supplier in China, a drug product applicant must refer to the "Technical Guidelines for Pharmaceutical Change Research of Marketed Chemical Drugs (Trial)". The applicant should first evaluate the risk level of the change to identify if it is a major, moderate, or minor change. The applicant must conduct the necessary research and submit the change application dossier to CDE according to corresponding change application requirements. For more details, please contact

Accestra team, and we will provide the necessary procedures and requirements.

Q22: Is it possible to include a packaging material or an Excipient not covered by a DMF in a Drug product dossier in China?

A22: If an AEP product doesn't have a DMF number in China, the dossier for the AEP can be submitted together with the drug product registration application. For AEP products, DMF is not mandatory.

Q23: In case that the microbiological testing for the release is outsourced to a Chinese CRO, should this information be included in the DMF? Moreover could this Chinese CRO be subject to inspection triggered by CDE evaluation of the DMF?

A23: Yes, the information about the Chinese CRO should be included in the DMF. In the event of an on-site inspection, the Chinese CRO may be subject to inspection by CFDI, although an AEP DMF usually does not trigger an on-site inspection. For more information on on-site inspections, please refer to Q6 in this document.

Q24: Where is the best place to get the continuous Regulatory updates? In addition, where is the best place to get the labelling requirements for clinical, API, medicinal/drug product and/or medical devices?

A24: Regulations and guidelines are published on various official websites such as NMPA, CDE, CMDE, CFDI, CDR, etc. Unfortunately, these regulations are not well-organized and may be updated from time to time. If you have any specific questions, please feel free to contact Accestra for assistance.

Q25: Could you please confirm if it would be acceptable by CDE to declare a range of possible quantities of API per drum (example: 0.5 kg/drum - 2.0 kg/drum) instead of specific numerical quantities of API per drum? (example: 0.5 kg/drum, 1.0 kg/drum, 2.0 kg/drum)

A25: For an API DMF, it is necessary to provide specific numerical quantities of API

per drum. Practically, a range is not acceptable, the solution is to submit many packaging sizes to cover different quantities.

Q26: Is there are specific test requirements for the primary packaging related to storage of API and finished product? Such as compatibility, leakage test etc. This could be for a solid, semi-solid or liquid form.

A26: Different types of packaging materials may be used for different APIs or finished products, and the risk level varies depending on the administration route. Therefore, it is recommended to evaluate the test requirements on a case-by-case basis for your specific product. For instance, stability data is required for polymer materials such as plastic and rubber. For packaging materials for injectables, compatibility and biosafety studies are required. On the other hand, for oral drug use packaging materials that are considered low-risk, compatibility and biosafety studies are not mandatory.

Q27: Is it common that the CDE asks for the Deficiency Letters received from other Regulatory Agencies?

A27. When filing DMF for APIs, there is no requirement to submit Deficiency Letters received from other regulatory agencies regarding the technical dossier. However, if Deficiency Letters were received from other regulatory agencies related to on-site inspections, they must be included in the DMF filing.

Q28: Which type of API DMF changes require QC samples / QC testing?

A28: When applying for a change to an API DMF, any modification that results in a change in specifications may trigger NIFDC sample testing. For more information on your specific situation, please contact the Accestra team.

Q29: For a clinical trial, do we need a review of the DMF in advance?

A29: If you are applying for a drug clinical trial, it is recommended that you review

the API dossier, if available, prior to submitting your application.

Regarding the DMF situation, if the API does not have a DMF number, it can be submitted along with the drug clinical trial application dossier. While an API DMF is not mandatory for a CTA application, the API dossier can also be submitted separately to the CDE by the API manufacturer or the appointed local agent, especially if there are confidentiality concerns. The Accestra team has extensive experience dealing with these application scenarios.

Q30: Does China recognize other countries' GxP? i.e. GLP, GDP, GCP, GMP etc. Countries such as USA, UK, EU, Japan etc.

A30: China has developed its own local GxP systems, which referenced a lot of the GxP systems in other ICH countries. As a result, these systems are generally aligned with the GxP requirements in countries such as the USA, UK, EU, and Japan. Since there are still some differences in the details between these countries, it is strongly recommended that applicants research China's local GxP systems and ensure compliance with them for imported products.

Q31: If the finished product specification does not include micro, do we need to include micro measurements per batch to align with the CP or can we present a risk assessment for skip testing or not performing the micro analysis?

A31: When registering an AEP in China, it's recommended that the product specification be compliant with ChP and national standards. This is a general requirement for CDE and NIFDC to evaluate the reasonability of the specification, especially for APIs. However, if it can be demonstrated that the product can meet the requirements of finished product manufacturers without including micro items in the specification, a risk assessment report can be submitted.

It's important to keep in mind that the intended use of the AEP may differ for different drugs, and micro testing may be required for other drug manufacturers. As such, AEP manufacturers may want to consider establishing a general specification that meets the requirements of ChP, EP, USP, and other relevant standards.