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CHINA CENTER FOR DRUG EVALUATION (CDE) Q&A ON DRUG APPLICATION

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China Center for Drug Evaluation (CDE)

Q&A on Drug Application

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Topic 1. The Submission and Acceptance of Drug Registration Applications

Q1: According to CDE's *Notice of Adjusting the Acceptance Methods and the Application Document Requirements During COVID-19 Pandemic*, should the applicant submit electronic application documents if the submission is after Feb. 7, 2022?

A1: If the applicant has submitted application documents in paper before Feb. 7, 2022, CDE will review the paper documents. If the registration application is found to be deficient in format review, the applicant should submit supplemental documents in paper in due time according to Article 85 of the *Administrative Measures for Drug Registration*.
If submitted after Feb. 7, 2022, only application documents in the electronic form will be accepted.

Q2: What differences are there between electronic submission and submission in eCTD format?

A2: According to *National Medical Products Administration (NMPA)'s Announcement on Adopting the eCTD Format for Drug Application* (No. 119 Announcement in 2021), only marketing authorization applications for class 1 chemical drugs, class 5.1 chemical drugs, class 1 therapeutic biological products, and class 1 prophylactic biological products can be submitted in eCTD format.

The *Notice of Adjusting the Acceptance Methods and the Application Document Requirements During COVID-19 Pandemic* applies to all drug applications accepted by NMPA.

Please don't mix up the two submission methods that are different in application scope and in technical requirements for compact disks.
Related Article: China to Accept eCTD Format for Marketing Authorization Applications for Specific Classes of Drugs; China Chemical Drug Registration Classification

Q3: Does the applicant need to submit the compact disk for drug registration inspection if the drug application is accepted after Feb. 7, 2022?

A3: If the applicant has submitted electronic documents in the compact disks according to the *Notice of Adjusting the Acceptance Methods and the Application Document Requirements During COVID-19 Pandemic*, it doesn't need to submit the documents or an additional compact disk for drug registration inspection.

But if the applicant submitted application documents in paper, it needs to submit the documents and an additional compact disk for drug registration inspection.

Q4: When the overseas originator drug or Chinese-domestically manufactured originator drug has been listed as a reference listed drug (RLD) but unavailable to the drug applicant, the drug applicant can choose the originator drug not imported to China as the RLD. In such a situation, can the applicant's generic drug be classified as a class 4 chemical drug?

A4: If the indication of the generic drug in the marketing authorization application is the same with the indication of the originator drug approved in China, the generic drug can be classified as a class 4 chemical drug for its application.

Q5: For a chemical drug marketed in China, how to submit the application for adding an indication approved in China and another indication approved overseas but not in China?

A5: To add an indication already approved in China, the applicant should submit a supplemental application. To add an indication approved overseas but not yet in China, the applicant should submit the clinical trial application and the marketing authorization application according to *NMPA's Announcement on Chemical Drug Registration Classification and Application Document Requirements* (No. 44 Announcement in 2020).

Q6: Can the applicant directly submit a marketing authorization application for a generic chemical drug?

A6: The appendix two to *CDE's Notice of Guidance for the Acceptance of Chemical Drug Registration Applications (Trial)* (No. 10 in 2020) stipulates that if after evaluation, a generic drug applicant is considered with no need or incapable to apply for clinical trials, and the applicant meets the conditions for clinical trial exemption, the applicant can directly propose marketing authorization for the generic drug and should specify the situation under "Other Items for Special Statement" in the application form.

Q7: Will the acceptance documents relevant to chemical API (active pharmaceutical ingredient)'s DMF (drug master files) filing be sent to the applicant?

A7: According to CDE's *Notice of Adopting the Electronic Administrative Authorization Documents for Chemical APIs*, applicants can print the acceptance documents via the "Applicants' Window" on CDE's website.

Q8: Should the applicant organize the chemical API filing documents according to the *Notice of Chemical Drugs' New Registration Classification and Application Document Requirements (Trial)* (No. 80 Announcement in 2016)?

A8: The applicant should conduct researches according to *NMPA's Notice of Chemical Drug Registration Classification and Application Document Requirements* and relevant technical guidelines.

It should organize the application documents with serial numbers according to the existing *M4 Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use*. The applicant can choose not to submit documents under the inapplicable items by marking them inapplicable, but need to specify the inapplicable reasons.

Q9: Can the applicant apply for adding a strength through generic drug marketing authorization application?

A9: No. According to *Administrative Measures for Drug Registration* and relevant regulations, the applicant should submit a supplemental application to add a strength.

Q10: How to apply for changing the dose, immune procedures, and target group of a marketed vaccine?

A10: According to *NMPA's Biological Product Classification and Application Document Requirements* (No. 43 Announcement in 2020), a vaccine with a changed dose and immune procedures belongs to class 2.5 improved vaccines, while a vaccine with a changed target group belongs to class 2.6 improved vaccines. To market a vaccine with these changes, the applicant should submit the clinical trial application and the marketing authorization application.

Q11: Is the applicant permitted to apply for license renewal earlier than six months before the oversea-manufactured drug's marketing authorization license gets expired?

A11: Yes, it is permitted.

Q12: How to continue with the drug application if the registration procedures have been terminated because the applicant fails to pay fees in time?

A12: According to *NMPA's Announcement on New Standards for Drug Registration Fees* (No. 75 Announcement in 2020), the registration procedures will be terminated if the drug applicant fails to pay fees accordingly. If the applicant intends to proceed with the application, it should re-submit the application according to the *Administrative Measures for Drug Registration*.

Q13: Can the applicant apply for priority review for a newly accepted application for a product manufactured on the same production line with

another product, or a re-submitted application that has been withdrawn before?
A13: The applicant should refer to the *Administrative Measures for Drug Registration* for priority review scope and the *Work Procedures for Priority Review of Drug Marketing Authorization Applications* for priority review procedures.
Related Article: Expedited Programs for Drug Registration-3.3 Priority Review

Q14: How to apply for marketing authorization for the combination therapy of two or more new molecular entity drugs whose clinical trials have both/all been approved? Does the applicant need to re-submit the application documents previously submitted for each single drug?

A14: As each single drug has not been put on the market, the applicant should submit new clinical trial applications for each drug separately and link the applications together.
Overlapping documents in the combination therapy (except clinically-mixed drugs) application and single drug application can be exempted from submission.

However, the pharmacological and toxicological evaluation of the combination therapy should be combined with each single drug's data. Therefore, all single drugs' pharmacology and toxicology documents should be submitted.

Q15: How to determine the registration classification of a generic chemical drug whose originator drug was marketed in China, and the originator's multiple generic versions have been marketed in China?

A15: Considering that the finished dosage forms (originator and its generic versions) with the same API already have complete and sufficient safety and efficacy data on Chinese people, the generic chemical drug can be registered as a class 4 chemical drug.

Q16: Which is the registration classification for a new dosage form (505b2) approved by FDA and listed as RLD and RS (reference standard) in the Orange Book? Class 5.1 or class 5.2?

A16: According to current regulations, such a drug belongs to class 5.1 chemical drugs.

Topic 2: Clinical Trial

Q1: Is it mandatory to submit manufacturing and testing standard procedures in the stage of applying for biological product clinical trial?

A1: No, it's not mandatory.

Q2: Researchers usually adopts a seamless design to connect different trials in the clinical research on a new antineoplastic drug. After getting the research data on a single drug, researchers may directly continue to explore the expanded use of the single drug and the combined use of the single drug with other drugs in the same research.

Thus, when the applicant submits the human clinical trial application for the first time, can CDE issue a notification that authorizes the clinical trials of both the single drug and its combination therapy?

A2: In the clinical trial plan submitted for the first time with the application, the applicant can include the single drug's dose escalation & expansion phase, and the exploratory phase of drug combinations.

However, when the plan has no data on the single drugs' pharmacokinetics, pharmacodynamics, safety, and tolerance, CDE can only evaluate the plan's partial content that focuses on the single drug but cannot give a conclusion on the reasonability and risks of the drug combinations.

According to Article 27 of the *Administrative Measures for Drug Registration*, the applicant should submit the clinical trial application for drug combinations after obtaining the single drug's data.

Q3: Should clinical trials be filed at the filing platform if they are initiated by applicants or researchers themselves?

A3: No, it's not necessary.
The filing platform mainly accepts filing for clinical trials or researches meeting any of the three conditions below:
(1) The applicant has received National Medical Products Administration (NMPA)'s clinical trial authorization document and the trial will be carried out in China.
(2) The applicant has filed the bioequivalence study on the chemical drug and got the filing number for the clinical trial.
(3) The applicant conducts the phase IV clinical trial and/or post-marketing researches according to the drug registration certificate or NMPA's notification.

Q4: When the clinical trial plan/information is public on the filing platform, does it mean that CDE has approved the plan/information?

A4: No. The applicant shall take the primary responsibility for filing drug clinical trial's

information according to existing laws and regulations. When necessary, the applicant should submit the clinical trial application & supplemental application, or communicate with CDE.

CDE will review the format and logic of the filed information, but it does not mean that CDE has reached a commitment, recognition, or contract with the applicant on the scientificity and reasonability of the clinical trial plan.

Q5: Does the applicant need to file the clinical trial result if the trial was completed before the *Administrative Rules on Filing and Publishing Drug Clinical Trial Information (Trial)* took effect on July 1, 2020?

A5: The applicant can refer to the table below:

Clinical Trial Completion Time	NDA	Filing Requirements
After July 1, 2020	Not submitted	Filing is mandatory within 12 months after completing the trial or before submitting NDA
Before July 1, 2020	Not submitted	Filing is mandatory within 12 months after completing the trial or before submitting NDA
	Submitted	Filing is optional

Q6: Can the applicant delete the filed information if it decides to terminate the filed international multicenter clinical trial that has started but not yet conducted in China?

A6: No. The applicant can only delete the filed information when the information is wrong or repeated. The applicant is not allowed to delete the filed information after getting the ethical approval or having filed the subsequent trial information. The applicant should update the information on the filing platform according to the real situation, e.g. to change the status to “terminated voluntarily”.

Q7: What are China’s requirements for the scope of submitting drug safety update reports (DSURs)?

A7: (1) Situations where DSUR submission is **mandatory**:

- The applicant shall submit DSUR if it conducts clinical trials that are permitted in the notification/approval documents for the clinical trial application, supplemental application, re-review application, marketing authorization application, and/or license renewal application.
- The applicant shall submit DSUR if it conducts phase IV clinical trial that is permitted in the approval document for the marketing authorization application. The clinical trial includes two specific situations: the applicant assumes it is necessary to file the clinical trial on the Drug Clinical Trial Filing and Information

Publicity Platform, and the applicant plans to submit the clinical trial's results as the feedback to the issues in the approval document or as part of the subsequent application.

(2) Situations where DSUR submission is **not mandatory**:

- In principle, the applicant does not need to file the bioequivalence (BE) study for the generic chemical drug's quality and therapeutic equivalence evaluation. But if the BE study meets the conditions in the Article 48 of the *Administrative Rules for the Quality of Drug Clinical Trials*, the applicant can consider submitting DSUR to CDE.

Q8: What is the scope of regional attachments 4 and 5 of DSUR? Should they cover the global information?

A8: DSUR's regional attachment 4 and 5 should include the information related to the clinical trial approved to be conducted in China, as well as the drug marketing authorization application to be submitted to China NMPA in the future.

Q9: When drug A's clinical trial has been approved and drug B has obtained marketing authorization in China, does the applicant need to submit clinical trial applications for both drug A and drug B to use them in a combination therapy?

A9: No, it is not mandatory to submit clinical trial applications for both drug A and drug B.

Q10: Is it mandatory for the applicant to apply for pre-IND meeting with CDE before submitting clinical trial applications for chemical drugs and therapeutic biological products?

A10: According to *NMPA's Announcement on Adjusting the Review and Approval Procedures for Drug Clinical Trials* (No. 50 Announcement in 2018), the applicant should apply for communication with CDE before submitting the clinical trial application for the first time. The specific rules are:

(1) For the **drug manufactured outside China**, the applicant can submit the drug clinical trial application after a self-evaluation of relevant risks if the clinical trial has been approved in a country or region with a complete drug regulatory system.

(2) For the drug whose applicant has been approved to conduct the clinical trial, the applicant can directly submit a new clinical trial application for **adding a new indication**. If the drug's previous clinical trial application has been submitted but not approved yet, the applicant needs to evaluate the relevant risks before submitting a new clinical trial application.

(3) NMPA recommends the applicant apply for pre-IND meeting with CDE before submitting the clinical trial application for a **biosimilar product**.

(4) Applicants of single agents in combination therapies should refer to the rules above.

Q11: As the trial is required to be conducted within three years after the applicant receives the clinical trial approval/notification document, what are the conditions for starting a clinical trial?

A11: According to the *Administrative Measures for Drug Registration* and NMPA's No. 46 Announcement in 2020, the approved clinical trial's approval document will expire if the trial is not started within three years after the approval. The approved clinical trial can start after the subjects sign the informed consent documents. The rule applies to all clinical trials approved before or after the *Administrative Measures for Drug Registration* took effect on July 1, 2020.

Q12: For a drug that has obtained marketing authorization outside China to treat acquired immune deficiency syndrome (AIDS), can the applicant directly use the clinical trial data acquired outside China to support the drug's marketing authorization application submitted to China NMPA?

A12: Such a drug can be reviewed and approved according to Article 2 of NMPA's *Announcement on Affairs Relevant to Optimizing the Review and Approval of Drugs* (No. 23 Announcement in 2018). If the applicant deems the data free from racial factors after conducting researches, the applicant can directly use overseas clinical trial data for marketing authorization in China.

Q13: Does *ICH M4: Common Technical Document (CTD) for the Registration of Pharmaceuticals for Human Use* apply to clinical trial applications?
A13: Yes, it does.

Q14: When the applicant is conducting the international multicenter clinical trials in China for a biological product imported to China, can the applicant conduct phase I clinical trial for the product at the same time?

A14: According to the *Decisions on Affairs relevant to Adjusting the Administration of Imported Drug Registration* (former China Food and Drug Administration, CFDI's No. 35 Announcement in 2017), the applicant is allowed to conduct international multicenter drug clinical trials in China and phase I clinical trials simultaneously. Drugs used in clinical trials are no longer required to be registered overseas, or have entered the phase II or III clinical trial. However, prophylactic biological product should still obey the previous requirement.

Q15: According to the *Decisions on Affairs relevant to Adjusting the Administration of Imported Drug Registration* (former CFDI's No. 35

***Announcement in 2017)*, the registration application for the imported drug can be directly approved if the drug is supported by international multicenter clinical trial data and is exempted from clinical trials in China. For such a drug, when should the applicant submit the application for verifying the drug's generic name?**

A15: For registration applications submitted during the interim period according to the *No. 35 Announcement*, the applicant can submit the generic name verification application in an official document to CDE in the review process. CDE will transfer the document to the Chinese Pharmacopoeia Commission to verify the generic name.

Q16: When the applicant has completed the approved phase I clinical trial, how should it apply for the subsequent clinical trials?

A16: The applicant should apply for phase II and phase III clinical trials through supplemental applications.

Q17: How should a clinical trial be filed after its approval document's ownership is transferred to another entity?

A17: The approval document's original owner should reserve the filing at the Drug Clinical Trial Filing and Information Publicity Platform and change the applicant. Please find out the specific steps at Help and Links on the platform.

Q18: Does the applicant need the certificate of pharmaceutical product (CPP) as a mandatory document for **applying for conducting international multicenter clinical trials for biosimilars in China?**

A18: According to the ***Decisions on Affairs relevant to Adjusting the Administration of Imported Drug Registration***, unless for prophylactic biological products, the applicant is allowed to conduct international multicenter drug clinical trials in China and phase I clinical trials simultaneously. Drugs used in clinical trials are no longer required to have completed overseas registration (CPP), or have entered the phase II or III clinical trial.

Q19: Can the applicant use a drug marketed outside China as the reference drug in the international multicenter clinical trial conducted in China?

A19: If the overseas-marketed drug has a same type of drug product marketed in China, the applicant can get the overseas-marketed drug via interim import and use it as the reference drug in the clinical trial. Otherwise, in general, the overseas-marketed drug should be registered in China before being used in clinical trials.

Q20: When a drug is marketed outside China only, what are the requirements and procedures for using the drug in a clinical trial?

A20: According to the *Announcement on Affairs Relevant to the Interim Import of Reference Drugs Needed in Researches* released in 2016, the applicant can apply for the interim import of drugs marketed outside China only. Only after the imported drugs are tested to be qualified, the applicant can use them in clinical trials.
Reference drugs should be registered and approved in China before they can be used as reference drugs in biological products' clinical trials. In principle, the products approved as biosimilars cannot be used as reference drugs.

Q21: Can non-clinical researches be exempted for chimeric antigen receptor T cell therapy (CAR T cell therapy) with existing clinical trial data?

A21: Non-clinical trials are for evaluating and controlling the risks of the clinical trial plan to ensure the subjects' safety. If the evaluated clinical trial data shows that the subjects' safety can be ensured, the CAR T cell therapy can be exempted from unnecessary animal tests in the investigative new drug (IND) application according to the principle that specific products should be analyzed based on their specific conditions.

Topic 3: Bioequivalence (BE) Study

Q1: What research documents should be included in the registration application for a drug proposed for biowaiver (waiver of the bioequivalence study)?

A1: The applicant should prove the drug's BCS (biopharmaceutics classification system) class according to the *Guidelines on the Waiver of Bioequivalence Studies in Humans*.

- For BCS Class I drugs, the applicant should conduct solubility, dissolution, and intestinal permeability researches.
- For BCS Class III drugs, in addition to the aforementioned researches, the applicant should ensure the proposed drug and the reference drug contain the same types of ingredients, and the ingredients in the proposed drug should be quantitatively similar to those in the reference drug.

The applicant should submit the application according to the drug's characteristics and documentation requirements.

Q2: For a drug without a clear BCS class, how should the applicant apply for waiver of the BE study?

A2: CDE advises that permeability data should be based on in vivo human data, and the relevant data in the originator drug's medication package insert, if any, can be used a reference. If the human data is insufficient, then in vitro permeability data can serve as supporting data.

Q3: Drug A has two strengths with proportional compositions, which means the ratio between the amount of excipient to the amount of active ingredient(s) is the same for both strengths. Because the stronger strength causes relatively stronger adverse reactions, FDA waives the BE study for the higher strength and permits the lower strength to be used in the BE study.

To apply for NMPA's marketing authorization of drug A's generic version, can the applicant conduct the BE study only on the lower strength version instead of the higher strength version?

A3: CDE advises the applicant to follow the *Technical Guidelines on Generic Drug Bioequivalence Studies in Humans with Pharmacokinetic Endpoints*, which allows the use of non-highest strength in BE studies if the highest strength has safety risks. Also, the test drug should meet the following conditions:

1. The test product has a linear pharmacokinetic profile;

2. For the test product and the reference product, their highest strengths and non-highest strengths have similar ingredient ratios*.

*Similar ingredient ratio refers to the following situations:

1) The ratios between all the active ingredient(s) and the inactive ingredient(s) are similar for different strengths;

2) For highly active drugs, where active ingredient(s) take a low percentage (e.g., the active ingredient(s) account for < 5% in the tablet core or the capsule contents);

i. The weights of different strengths are the same, with deviation rate lower than 10%;

ii. All the strengths use the same type of inactive ingredient(s);

iii. The differences between strengths lie in the different amounts of active ingredient(s) and the different amounts of one or more inactive ingredients.

3. According to the dissolution test, the test product has a similar dissolution profile to that of the reference product's highest strength.

Q4: Is unfed bioequivalence study an indispensable part of the bioequivalence study?

A4: According to *Technical Guidelines on Generic Drug Bioequivalence Studies in Humans with Pharmacokinetic Endpoints*, the applicant can skip the fed bioequivalence study if the reference drug's medical package insert specifies that the drug can only be taken in an unfed state (1 hour before meal or 2 hours after meal).
For immediate-release oral drugs, it is recommended that the applicant should conduct both unfed and fed bioequivalence studies, unless the unfed one has severe safety risks.
If there is sufficient data proving the severe safety risks with the unfed dose, the applicant only needs to conduct the fed bioequivalence study.

Q5: Will the clinical trial approval document be invalidated if the approved drug's manufacturing technique changes before the bioequivalence study?

A5: In general, the approval document remains effective if NMPA doesn't give special requirements in the document.

Q6: Is it mandatory for the company to get GMP certificate before manufacturing the investigational drug samples for the bioequivalence study? Should the drug manufacturing license cover the investigational drugs?

A6: According to the current regulations and technical guidelines, investigational drug samples should be manufactured on the drug's actual production line or in middle or larger scale GMP-compliant factories for trial production. The investigational drug's production scale should be middle or larger, with the same manufacturing techniques used in mass production and the manufacturing process following the GMP.

Q7: Among the 289 drugs that were required to complete the quality and therapeutic equivalence evaluations before the end of 2018, 48 drugs were selected by the former China Food and Drug Administration (CFDA) to formulate the draft *List of Drugs Whose Bioequivalence Studies in Humans Can Be Waived or Simplified*. In the draft, CFDA mentioned that "bioequivalence studies can be waived if the applicant conducts pharmaceutical equivalence evaluations". In this context,

1. If the applicant has decided to use the pharmaceutical equivalence evaluation, is it still mandatory to submit the high solubility data and high

permeability data according to *Guidelines on Waiving Bioequivalence Studies in Humans*?

2. If the applicant needs to submit the high permeability data, does it need to submit human pharmacokinetics research materials as well? Can the applicant use the pharmacokinetics data from the originator drug's medical package insert?

3. Does the applicant need to submit the document which specifies how the excipient affects the absorption?

A7: The answers to the three questions are as follows.

1. For BCS Class I drugs applying for biowaivers, the applicant should submit the solubility and permeability data according to *Guidelines on Waiving Bioequivalence Studies in Humans*.

2. Human pharmacokinetic study is the most direct and effective method for proving high permeability. Pharmacokinetics data in the originator drug's medical package insert can support the permeability. If there is in vivo human pharmacokinetic data, whether sufficient or not, it should be submitted.
When in vivo human pharmacokinetic data is insufficient, in vitro permeability data, e.g., Caco-2 assay data, can also be the evidence for permeability. When necessary (e.g. there is no in vivo human pharmacokinetic data or any other data for proving high permeability), the applicant should submit extra literature to prove the permeability.

3. For BCS Class I drugs which apply for biowaivers and are different in excipient type and amount from the reference drug, the applicant should submit data to prove the excipient's effect on the absorption.

Q8: When designing the bioequivalence study for a highly variable drug, how can the applicant adjust the bioequivalence criteria appropriately according to the reference drug's intra-subject variability?

A8: The applicant can design the study according to the reference-scaled average bioequivalence (RSABE) statistical method recommended by US FDA's guidance. But before adopting the RSABE method, the applicant should analyze the reason for the drug's high variability, and evaluate and demonstrate the applicability of the method in the BE study based on the existing researches and literature. In addition, the applicant should specify the statistical method in the clinical trial plan and the statistics plan.

Q9: What are the requirements for the stability study, which should be included in the documents for filing chemical drug's bioequivalence study?

A9: According to the BE study filing regulations, the stability research data should cover at least three batches of self-made samples from the mid-or-above size trial production, including but not limited to samples from mid-to-larger-size trial production and samples produced for the BE study. The accelerated and long-term stability research on the samples should last for at least three months before the bioequivalence study with recorded experimental data, and continue during the study.

Q10: Can the applicant use the reference listed drugs / test drugs from different production batches for unfed and fed bioequivalence respectively in the same bioequivalence study?

A10: No, the reference listed drugs / test drugs to be used in the same bioequivalence study should come from the same batch.

Topic 4: Selection of Reference Listed Drugs

Q1: How should the injectable drug's marketing authorization holder select a reference listed drug (RLD) to conduct the quality and therapeutic equivalence evaluation?

A1: According to China NMPA's *Announcement on Conducting Quality and Therapeutic Equivalence Evaluations of Generic Versions of Injectable Chemical Drugs*, the MAH should select RLD from the RLD Catalog issued by NMPA, conduct therapeutic equivalence researches, and apply for the equivalence evaluation.

Q2: Does the generic drug company need to buy a new RLD if the previously bought RLD's manufacturer and MAH both changed?

A2: From the perspectives of drug lifecycle management and risk control, the applicant should decide whether to buy a new RLD based on the research result and the situation after the changes.

Q3: When developing a generic drug, what if the applicant cannot conduct the stability study starting from the production date because a period of time has passed when the applicant receives the RLD?

A3: According to former CFDA's *Application Documentation Requirements for Chemical Drugs Under the New Registration Classifications (Trial)*, the applicant should summarize the samples' conditions in the stability study as well as the study's conditions, indicators, and result, analyze the changing trend, and propose the drug's storage conditions and expiration date. The applicant should also compare the generic drug with its originator version and the drug with the same nonproprietary name listed in the Chinese Pharmacopoeia (ChP). The generic drug should have no lower stability than the originator drug and ChP-listed drug.

Q4: It is mandatory to select the RLD same to the RLD recommended by NMPA (formerly CFDA)?

A4: The applicant does not have to choose RLDs from the RLD lists released by former CFDA. Instead, the applicant can choose the product considered to be equivalent to the RLD to perform as the reference drug according to NMPA's *Statement on the Published RLDs* (hereafter referred to as the *Statement*).
If the equivalence is too difficult to be proved / is wrong according to the *Statement*, but there is enough evidence to support the equivalence, the applicant can submit an official document, including the chosen drug's detailed information and relevant materials, to specify the difficulty to prove the equivalence and propose a solution to the Equivalence Evaluation Office, then the Office will discuss the matter with the applicant.

Q5: For a drug without recommended RLDs in the RLD Catalog, if the company filed for a proposed RLD to CDE, what will CDE do about the proposal?

A5: For drugs without recommended RLDs, CDE will regularly discuss the proposed RLDs with experts according to the RLD selection principles in the former CFDA's *Announcement on the Work Items about Quality and Therapeutic Equivalence Evaluations of Generic Drugs* (No. 100 Announcement in 2017). Based on expert's opinions and the review of new generic versions under the same nonproprietary name, CDE will publish the official RLD lists regularly.

Topic 5: Quality and Therapeutic Equivalence Evaluation

Q1: If the generic injection is different from the RLD in strength, can the injection be applied for the quality and therapeutic equivalence evaluation?

A1: There are three situations:

1. If the solution injection and the RLD have the same concentration rate but different volumes, the solution injection can be accepted for the evaluation. After clinical review, NMPA will conduct the equivalence evaluation of the strength within the permitted scope, and approve the equivalence evaluation if the strength meets the requirements.

2. Solution injection which has a different concentration rate from the RLD can be accepted for the equivalence evaluation. The technical review should cover whether the strength is proper considering the clinical usage and dosage. The recognized strength should be reviewed according to the quality improvement requirements. The strength that passes the technical review will not be considered as having passed the equivalence evaluation.

3. Powder injection, in which the strength is equivalent to the volume, can refer to the first situation above.

Q2: Can the supplement application for adding a new strength submitted together with the application for equivalence evaluation?

A2: As equivalence evaluation is administered under the proprietary names of different drugs, the applicant can directly submit the equivalence evaluation application for adding a new strength to the drug under the same nonproprietary name. To prevent the misuse of the strengths, the new strength should be within the scope for reasonable clinical usage and dosage, and equivalent with the originator drug or the RLD.

Q3: How should the marketed drugs apply for equivalence evaluation if they are not within the scope of filing BE studies?

A3: According to the *Announcement on Filing Bioequivalence Studies on Chemical Drugs*, the drugs belong to the following five categories*, to seek equivalence evaluation, should first submit supplemental applications. With the approved supplemental application, the applicant can conduct the clinical research, then apply for equivalence evaluation after completing the research.

*Five categories:
1. Radioactive drugs, anesthetics, class 1 and class 2 psychoactive drugs, and chemical precursors.
2. Cytotoxic drugs.
3. Drugs not applicable to be verified the quality and therapeutic equivalence to RLDs by BE tests.

4. Drugs used in BE tests not aiming for drug registration in China or the quality and therapeutic equivalence evaluation of generic drugs.
5. Drugs considered by the applicant to have potential safety risks in the BE tests and need technical evaluation.

Q4: For drug approved under the new registration classifications, do they need to apply for equivalence evaluations?

A4: For new drugs applying for approval under the new registration classifications, they already have safety and efficacy evidence. For generic drugs applying for approval under the new registration classifications, they will be accepted and reviewed according to the principle that they are equivalent to the originator drug in quality and therapeutic effect.

For new drugs and generic drugs mentioned above, they don't need to go through equivalence evaluations. After approval, they will be included in China Marketed Drug Catalog.

Q5: According to Article 8 of the former CFDA's Announcement on the *Work Items about Quality and Therapeutic Equivalence Evaluations of Generic Drugs* (No. 100 Announcement in 2017), if seeking the drug's marketing authorization according to the equivalence evaluation's standards, the applicant should evaluate whether the drug complies with the current requirements for the equivalence evaluation in the technical guidelines.
If the drug meets the requirements, the applicant can apply for waiving the equivalence evaluation. NMPA will review the waiver application according to the technical requirements for the equivalence evaluation, with particular attention to the authenticity and integrity of the data in the original marketing authorization application.

For a drug that obtains marketing authorization via the approach above, how can the applicant apply for waiving the equivalence evaluation?
A5: The applicant can submit a supplemental application for the waiver.

Q6: According to the former CFDA's *Application Documentation Requirements for Chemical Drugs Under the New Registration Classifications (Trial)* (No. 80 Announcement in 2016), the applicant should summarize the samples' conditions in the stability study as well as the study's the conditions, indicators, and result, analyze the changing trend, and propose the storage conditions and expiration date. The applicant should also compare the generic drug with its originator version and the drug with the same nonproprietary name listed in the Chinese Pharmacopoeia (ChP). The generic drug should have no lower stability than the originator drug and ChP-listed drug.

However, the generic drug company receives the RLD when half a year to one year has passed since the production of the RLD. In such a case, can the RLD's production date be considered as the starting date of the RLD's subsequent stability study?

A6: CDE advises the applicant to conduct stability study on the proposed drug according to stability study's guidelines. It is not mandatory to conduct the stability comparison study on both the proposed drug and the RLD.

Q7: Does the applicant need to conduct allergy, irritation, and hemolysis tests for injections undergoing equivalence evaluations?

A7: The tests are required if the manufacturing technique changes, but are not required if the injections already have clinical safety data.

Topic 6: Biological Product R&D

Q1: What are the requirements for the manufacturing site to be used in clinical trials for cell therapy products? What about process control?

A1: **Viruses and cells** used in human clinical trials should be produced in compliant with pharmaceutical GMP. As for **plasmids** used in production, the requirements depend on specific use conditions. If the plasmids are directly used as vectors for in vitro genome editing, they are recommended to be produced in GMP-compliant conditions.

Applicants are required to **control the manufacturing process** in accordance with China's current GMP and can refer to other countries' and regions' GMP for cell therapy products. Cell therapy products can neither tolerate the virus inactivation processes, nor go through terminal sterilization or sterilization filtration. Therefore, it is particularly important to control their manufacturing process.

In appropriate stages of the manufacturing process, applicants should establish testing items and acceptance criteria for process control, to ensure that the product's manufacturing process is comprehensively monitored and the quality control is consistent between different production batches.

In addition, considering the manufacturing techniques, equipment, operations, and administrative standards, applicants should formulate measures to prevent the

confusion, contamination and cross-contamination of different batches of products, and ensure the traceability of the whole manufacturing process (from tissue/cell collection, production, transportation, to clinical use).

Q2: Can animal/human serum be used in the culture of cell therapy product?

A2: Animal/human serum should be avoided as much as possible in the manufacturing of cell therapy products. If the animal/human serum is necessary, the applicant should provide sufficient research materials specifying the necessity of using the serum in cell culture. After validating the necessity, the applicant should provide the reasons for choosing a certain type of serum and using a specific amount, and clarify the serum's source and quality standards. The applicant should establish a quality control system, test the residues, and evaluate safety risks. In the technical review, CDE will evaluate the risks and benefits comprehensively considering the product's value in clinical use.

CDE advises the applicant to learn about serum safety validation requirements referring to *Technical Guidelines on Cell Therapy Product Research and Evaluation*. In addition, CDE encourages the applicant to actively explore for safer serum substitutes with clearer compositions to be used in future production.

Q3: What are the requirements for bacterial strains for plasmid production and cells for packaging viruses?

A3: The applicant should use the strain or cell which has clear culture, legal source, as well as quality good enough for the R&D phase, and the safety of the final product. CDE advises the applicant to provide the traceability information according to the specific purchase channel. The information includes but is not limited to certificate documents, culture process, passaging, and assay.

CDE also suggests that under the precondition of fulfilling the Chinese Pharmacopoeia standards and ICH guidelines, the applicant should establish a strain/cell bank according to the product's actual conditions and test the strains/cells comprehensively.

Q4: Currently, the lentiviral packaging system is usually the third-generation four-plasmid virus packaging system. Is it permitted to use the second-generation three-plasmid lentiviral packaging system?

A4: In chimeric antigen receptor (CAR) T cell products, lentiviral vectors are often used to introduce target genes. The reverse mutation of lentiviral vectors and the insertion of viral genes into the human genome, which are intrinsic risks in the use of CAR T products, should be considered in product design and quality control, and kept

under long-term monitoring in subsequent researches.

The four-plasmid lentiviral packaging system further deletes unnecessary elements for viral packaging, restructures related gene sequences, and separates multiple genes for expression on different plasmids. As a consequence, the possibility is reduced for lentiviral reverse mutation and homologous recombination. Therefore, if the applicant intends to use the lentiviral system, CDE recommends safer plasmid system for packaging lentiviruses, and viral vectors with self-inactivating (SIN) structures.

If using a higher-risk plasmid system, the applicant should evaluate the potential risks and explain the rationality of using this system. If sufficient evidence cannot be provided, CDE advises the applicant to conduct safety studies.

Q5: In terms of testing sterility, mycoplasma, replication-competent lentivirus (RCL), and other safety indicators, can the applicant use new self-established method to replace the conventional methods in the Chinese Pharmacopoeia or general guidelines for the testing before product release?

A5: Based on the characteristics of cell therapy drugs, the applicant can develop new sterility and mycoplasma testing methods for the testing before product release, but the new methods should be fully validated.

It should be noted that when the new method is not fully validated that it can replace the traditional methods in the Chinese Pharmacopoeia, it is recommended to use the traditional method for parallel testing while using the new testing method before product release. CDE also suggests the applicant collecting data of different testing methods during clinical trials, conduct complete methodological research and validation, and submit research data in subsequent applications.

In addition, while using the new and conventional methods in parallel, if the cellular drug must be used on humans as soon as possible while there is inconsistency between the testing results of the two methods, the applicant should formulate emergency remedial measures in advance.

As RCL is an important safety risk concern, when applying for clinical trials, it is recommended that the applicant should use the validated cell culture method in the general guidelines to complete the RCL testing for virus (supernatant and end-of-production cells).

For final cell products, the applicant can use a methodologically validated rapid method for RCL testing before product release, and the samples should be kept. When necessary, the applicant should use the indicator cell culture method for

retrospective testing and analysis. In addition, the applicant should monitor the RCL during the production process. For products with higher risks (such as products based on the selection of plasmid systems), the RCL testing requirements should be appropriately higher.

The applicant should set reasonable positive and negative controls for each batch of cell culture testing. The testing method's sensitivity and sample numbers should meet the safety requirements based on the dose used in clinical research. Also, the applicant should consider the virus particles' inhibitory effects on RCL testing.

Q6: How to conduct the stability study for cell therapy product in the clinical trial application stage?

A6: CDE recommends the applicant to design stability study plan according to ICH Guideline Q5C, *Technical Guidelines on Biological Product Stability Studies*, *Technical Guidelines on Cell Therapy Product Researches and Evaluations*, and *Key Points for Cell Therapy Products' Pharmacological Studies and Documentation for Clinical Trial Applications.* The plan should cover the research's product batches, research conditions, testing items, and testing frequency.

In clinical trial application, the cell product's stability study document should cover all the stages of storage, transportation, and use of the samples. After meeting the basic requirements for clinical use, the applicant can enrich and improve the stability study during the clinical trial.

CDE advises the applicant to conduct researches on representative samples according to the specific cell therapy products' availability. The samples include the collected tissue/cell samples, intermediate samples during the production, final cell products, samples in clinical use, etc. The samples' cell densities and volumes should be able to represent those in actual production and use.

The applicant should also design the stability study plan based on the cell therapy product's characteristics. For example, if the product is a liquid dosage form, the applicant should pay attention to vibration's impact on cells. If the product is a frozen dosage form, the applicant should study how cryopreservation and restoration affect the cells.

Q7: What information should be included in the safety evaluation and compatibility research on the containers and packaging materials with direct / short-term contact with the cell therapy product?

A7: For the clinical trial application, CDE advises the applicant to provide basic information, including the container's and packaging material's sources, quality

standards, biological safety research data, etc.

CDE also advises the applicant to complete the preliminary evaluation of compatibility between the product and the packaging container (small-sized container of the same material with the bigger ones is also acceptable) before applying for clinical trials. The applicant should ensure the safety of clinical use, with particular attention to the compatibility between cells/excipients (such as dimethyl sulfoxide, also known as DMSO) and containers, and the corresponding safety risks.

On the premise of ensuring the safety of the samples for clinical trials, the basic performance testing and the packaging material's biological evaluation conducted by the supplier, as well as the preliminary stability study results that meet the clinical trial needs, can be used as the references for evaluating the compatibility of packaging materials.

During the clinical trial, the applicant should conduct a complete compatibility study according to the composition and storage conditions of the cell preparation following the relevant guidelines.

Q8: For biological products that obtained marketing authorization outside China, are they permitted to be imported for one time to be used as the reference drugs in clinical trials?

A8: According to NMPA's *Announcement on the Items Relevant to One-time Import of Biological Reference Products Used in Clinical Trials* (No. 94 Announcement in 2018), products of the two categories below can be imported for one time:

1. Originator biological products that have obtained marketing authorization in China, but the drug R&D institutes or manufacturing companies are not able to obtain them immediately on the Chinese domestic market;
2. Originator biological products that have obtained marketing authorization outside China, and obtained the clinical trial authorization in China.

Q9: Is a new nonclinical trial mandatory for a biological product with technology transferred from overseas to China?

A9: For biological product changes, the applicant should conduct sufficient technical evaluation and verification. Comparability research is the basis and key to a successful evaluation of biological product changes. The research aims to confirm whether the changes have adverse effects on quality, safety, and efficacy of biological products by collecting relevant technical data and analyzing them in comparison.

The applicant does not need to conduct post-change nonclinical/clinical studies if the before-after comparability is proved by sufficient analyses on the manufacturing

process, quality attributes, and stability studies.

The applicant needs to conduct bridging or confirmatory clinical trials if the non-clinical trial research cannot prove the changes' effects on product safety and efficacy because of the following three circumstances:

① Quality analysis and comparison results are not accepted;

② There are major differences between the pre- and post-change products; or

③ There are deficiencies in the comparability research projects.

Proving comparability does not mean the quality attributes are exactly the same in pre- and post-change products, but they should be highly similar. Also, based on the existing knowledge and research results, the evidence is sufficient for predicting that the quality attribute change won't have any adverse effects on product safety or efficacy.

Topic 7: Associated Review and Approval of APIs, Excipients, and Packaging Materials

Q1: If the applicant has filed the drug master file of the active pharmaceutical ingredient (API) according to former CFDA's *Announcement on Adjusting the Review and Approval of APIs, Pharmaceutical Excipients, and Packaging Materials* (No. 146 Announcement in 2017), how should the applicant apply for independent review of the API according to Article 43* of the *Administrative Measures for Drug Registration*?

**Article 43 stipulates that APIs that are generic versions of APIs in the marketed drugs in China can apply for independent review and approval.*

A1: For API that has obtained a filing number according to the No. 146 Announcement, the applicant can apply for changing the review procedure by using the "Already Filed. Apply for Review" function under the item with the corresponding filing number, if the API meets either condition below:

1. The API's filing number has not been associated with the finished dosage form's review.
2. The API has completed the associated review together with the finished dosage form, but the API's filing status is marked as "I (inactive)" in the associated review conclusion.

If meeting either condition above, the applicant should choose whether the application materials have any change from the filed materials when applying for post-filing review. For materials without changes, the applicant should submit the "re-filing commitment letter" to CDE; for materials with changes, the applicant should re-submit a complete set of application materials according to current requirements.

In addition, the applicant should make sure that the filed chemical API has been accepted by CDE before choosing it for the associated review for the marketing authorization application of the finished drug product. For chemical APIs that have been filed according to No. 146 Announcement, the applicant can change the review procedure via "Already Filed. Apply for Review" function.

Q2: How to file for the same API with different manufacturing processes?

A2: In principle, the filer should file for the API under different filing numbers and submit filing documents separately.

Q3: If the finished dosage form applicant chooses to use the API manufactured outside China and without being filed in China, can the API supplier submit the confidential data by itself without disclosing them to the applicant who submits the registration application of the finished dosage form?

A3: According to NMPA's *Announcement on the Items Relevant to the Associated Review, Approval, and Supervision of Drugs* (No. 56 Announcement in 2019), for APIs, excipients, and packaging materials (the three altogether referred to as AEPs) that cannot be filed at CDE's platform due to special reasons, the finished dosage form applicant can submit the AEP research data together with the finished drug application to CDE.

For convenience, the API data (including confidential information) can be directly sent by the overseas API supplier to CDE. But the API documents should be associated with the finished dosage form's application documents. The finished dosage form's name, the application item, the applicant's name, and contact person, and contact details, etc. should be specified in the documents. The application which passed the format review will be accepted by CDE.

Topic 8: Requirements for Changes

Q1: When applying for renewing the license of an imported drug, can the applicant apply for the change of the drug's strength at the same time?

A1: No, the applicant is not allowed to do so. According to the former CFDA's *Announcement on Items Relevant to License Renewal of Imported Drugs* (No. 18 Announcement in 2009), it is not allowed to apply for renewing an imported drug's license and changing the manufacturing site / strength at the same time. To change the manufacturing site / strength, the applicant should submit an independent supplemental application.

Q2: During the drug review, how to submit an application for changing the applicant?

A2: Please refer to the table below:

Applicant name change	Applicant entity change	Technical change (e.g., manufacturing site change)	Application
Yes	No	No	According to the former CFDA's *Announcement on Further Regulating the Acceptance of Drug Registration Applications* (No. 122 Announcement in 2015), the applicant can submit the **change application** to the regulator which previously accepted the corresponding drug registration application. - If the drug registration application was accepted by the provincial medical products administration, then the change application should be submitted to the corresponding medical products administration, which will report to CDE about the change. - If the drug registration application was accepted by CDE, then the change application should be submitted to CDE, which will directly change the information.
Yes	Yes	No	Same as above.
Yes	Yes	Yes	The new applicant should submit a supplemental application. After being accepted, the supplemental application should be reviewed in association with the drug registration application.

Q3: What category does the change of drying method from tray drying to fluid

bed drying in the chemical drug manufacturing process belong to?

A3: As the change from tray drying to fluid bed drying may have significant impacts on the product quality, such a change belongs to Category III (major) changes as per the *Technical Guidelines on Researches on Changes to Chemical Drug With Marketing Authorization*. Also, the change of drying method may impact the drug's bioavailability. Therefore, for oral solid drugs difficult to dissolve, the applicant needs to conduct the bioequivalence study before changing the drying method.

Q4: What kind of application should the applicant submit for changing the manufacturing site of the API used in the imported finished dosage form?

A4: Changing the API's manufacturing site may have influences on the finished dosage form's quality. CDE advises the applicant to submit a supplemental application that needs technical review.

Q5: Should the applicant submit an application for adding a strength if it adds a strength for the tablet core of a sugar-coated chemical drug?

A5: CDE advises the applicant to submit an application for changing the manufacturing process.

Q6: Can the application for changing the marketing authorization holder and the manufacturing site be combined with the application for imported drug license renewal?

A6: According to the *Announcement on Items Relevant to License Renewal of Imported Drugs*, the license renewal applications for an imported drug should not be combined with supplemental applications. To change the manufacturing site or add a strength, the applicant should submit independent supplemental applications.

Topic 9: Other Q&As

Q1: Can a foreign company's resident representative office perform as an agency for the foreign marketing authorization holder (MAH) in China?

A1: No, they cannot. According to *Administrative Measures for Drug Registration*, a foreign applicant should appoint a legal corporate entity to carry out affairs related to drug registration. The *Administrative Provisions on Filing for Permanent Agencies of Foreign Companies* stipulates that foreign companies' resident representative offices

are not legal corporate entities and can only engage in non-profit activities related to the foreign company's businesses in China.

Q2: Can manufacturing process exploration and manufacturing condition establishment be placed during the clinical trial?

A2: When applying for clinical trial, the applicant should determine the steps, parameters, and production process control measures of the cellular drug's manufacturing process that is compatible with the clinical trial. The manufacturing process should be evaluated in terms of its transfer from being used in the laboratory to being used in the human clinical trial. The applicant should support the reasonable and steady manufacturing process to meet the supply of cellular drugs during the clinical trial, and ensure the product safety and the process & quality controllability.

It is also necessary to compare and analyze the differences and commonalities between ①the non-clinical animal research and the non-registered clinical trial (if applicable) and ② the clinical trial in terms of manufacturing process (in a broad sense, including manufacturing process, site, raw materials, and scale) and product quality. If there are quality differences, the applicant should further analyze and evaluate whether it is necessary to conduct relevant bridging studies or restart researches on manufacturing processes for clinical trials. If there is a need for changing the manufacturing process during clinical trials, it is recommended for the applicant to refer to ICH Q5E Guidelines and other relevant Chinese/international technical guidelines to conduct sufficient researches on the changes. The applicant should analyze the comparability of product safety, efficacy (based on specific situations), and quality controllability before and after the changes.

If it is truly necessary to change the critical manufacturing processes and parameters during the clinical trial, the applicant should fully analyze and evaluate the comparability before and after the changes. When necessary, the applicant should conduct bridging clinical trials on animals or humans. It is encouraged that the drug R&D institutes communicate with CDE about the research plan on changes.

Q3: How to verify the non-proprietary name of the proposed drug during the review of the drug registration application?

A3: For registration application under review and considered that it needs drug nonproprietary name verification after the technical review, CDE will notify the applicant to submit documents for verifying the drug's non-proprietary name. The applicant can also send an application to CDE for verifying the name.

Q4: How to apply for changing the registration agency of an imported drug?

A4: According to the *Announcement on Items Relevant to Imported Drug Registration*, the applicant should report to NMPA about the supplemental information of changing the imported drug's registration agency.

Q5: Should all the application dossiers for imported drugs be translated into Chinese?

A5: According to *Administrative Measures for Drug Registration*, all the application dossiers should be in Chinese, with the attached version in the original language. Chinese translation should be consistent with the original texts. Documents in neither Chinese nor the original language can be an appendix for reference.

Q6: The marketed innovative monoclonal antibody (mAb) products for which crab-eating macaques are used in the long-term toxicity experiments as part of the pre-clinical safety evaluation. Is it permitted to use only one species related to crab-eating macaques in the pre-clinical safety evaluation of the proposed product which is the same type of the marketed mAb products?

A6: In the preclinical safety evaluation of new mAbs, the applicant needs to consider the selection of animal species, and choose relevant animal species for preclinical research. If there is only one animal species, it is permitted to choose them for the subsequent long-term repeated-dose toxicity experiment. However, it is recommended to include toxicity studies on the second animal species in the early-stage dose-finding toxicity studies to determine the toxicity. The inclusion is meaningful for evaluating off-target toxicity.

Q7: When the impurity limit changes in new drug development, should the applicant conduct the non-clinical pharmacology and toxicology bridging studies?

A7: The total amount of impurities in the human test is supported by the corresponding data in the animal test result. If the animal test is necessary, the applicant should refer to ICH Q3 Guidelines to carry out a repeated-dose toxicity test which usually lasts 14-90 days.

Q8: Should every single unit of suppository in the package be printed with the approval number?

A8: Though there are no definite regulatory requirements in this regard, it is advised to print the approval number on each level of packaging, including the minimum packaging unit, for the sake of managing drug usage and controlling risks.

Q9: For the application of a drug imported to China, what are the requirements for drug manufacturers to use the US FDA's GMP inspection report as the GMP compliance evidence?

A9: Overseas regulator's GMP inspection report is accepted for imported drug registration. The drug manufacturer should ensure that the information on the report is consistent with the application. In addition, the report should be notarized by both a notary institution in the country from which the drug is imported and the country's embassy in China.

Q10: Does CDE accept the electronic GMP certificate from the website of France's National Agency for the Safety of Medicines and Health Products (L'Agence nationale de sécurité du médicament et des produits de santé or ANSM)?

A10: Yes, the certificate is accepted by CDE.

Q11: How to submit applications for drug-device products without marketing authorization in China?

A11: According to the *Announcement on Items Relevant to Drug-device Combination Product Registration* (No. 52 Announcement in 2021), the applicant should send an application to the Center for Medical Device Standardization Administration of NMPA for determining the drug/device category of the product. After the category is determined, the applicant can apply for product registration and specify that it is a "drug-device combination product" in the application form.

Q12: How to apply for registration of drug-device combination product mainly functioning as a drug?

A12: According to the *Announcement on Items Relevant to Drug-device Combination Product Registration* (No. 52 Announcement in 2021), the applicant should apply for registering the product as a drug and identify it as "drug-device combination product" in the application form. For application documentation requirements, the applicant should refer to *Chemical Drug Registration Classification and Application Dossier Requirements* or *Biological Product Registration Classification and Application Dossier Requirements*.

About BaiPharm

BaiPharm offers a full portfolio of China NMPA compliance consulting services and cross-border e-commerce (CBEC) marketing solutions. With our senior expert team, we ensure professional response and full support for clients.

Our experts have a thorough understanding of pharmaceutical regulations and profound knowledge of CMC research, pharmacodynamic evaluation, clinical trial, quality assurance & control, and facility validation. We are fully qualified to engage in China market entry projects for finished drugs, APIs, excipients, and packaging materials.

Our Services

Drug Application

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Local Agency Support

Serving as overseas drug marketing authorization holder (MAH)'s local agency in China, and fulfilling obligations throughout the entire lifecycle of the drug product

Pharmacopoeia Translation

Translating Chinese Pharmacopoeia standards, covering chemical drugs, biological products, active ingredients, excipients, packaging materials, testing methods, and guidelines

Pharmacovigilance

Offering pharmacovigilance services, including making safety & risk management plans, collecting, entering and evaluating data, following up safety cases, and preparing safety reports

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