Importing Pharmaceutical Products to China

Imported drugs need pre-market approval before entering the Chinese market

Drugs imported for human use are required to obtain pre-market approval from the China Food and Drug Administration (CFDA) before being placed on the Chinese market. This requirement applies to all drug products (medicines), including innovative drugs and generic or over-the-counter (OTC) drugs. A drug substance or active pharmaceutical ingredient (API) also requires pre-approval by the CFDA.

The definition of "drugs" in China covers chemical and biological products (vaccines, blood products and biotech products, etc.) and herbal medicines. Pharmaceutical products are commonly referred to as "chemical drugs" under Chinese legislation.

The main focus of this guide will be on imported chemical drugs for registration in China. For overall consistency, the term "pharmaceutical products" is used throughout this guideline, with other types of drugs referred to specifically. A summary of biological products and the differences between the registration requirements of chemical drugs is provided in this report.

Imported pharmaceutical products are subject to drug registration rules that are based on the Chinese Drug Law and its implementation regulation. The *Drug Administration Law of the People's Republic of China* (2001, slightly revised in December 2013) and the *Regulation for Implementation of the Drug Administration Law of the People's Republic of China* (2002) set out the general principles for pharmaceutical registration in China.

Furthermore, the implementation regulation *Measures of the Administration of Drug Registration***(2007) outlines the detailed technical requirements and procedure for application and approval.

The Chinese State Food and Drug Administration (SFDA) formally changed its name to the China State Food and Drug Administration (CFDA) in 2013 (www.cfda.gov.cn).

CFDA is a full ministry agency reporting directly to the State Council, which is China's highest administrative body. The CFDA is the competent authority responsible for registering and handling applications for imported pharmaceutical products.

Under the CFDA, there are two departments responsible for drug products:

- The Drug and Cosmetic Registration Management Department, which ensures all licensing and manufacturing standards are adhered to and to optimise the registration system
- The Drug and Cosmetic Supervision Department, which oversees regulatory duties to ensure all standards are adhered to, reacts to reports of adverse drug effect cases and adverse drug reactions. The department also reports on recent events within the sector and monitors the sector.

This new structure has combined licensing and certifications into a single certificate to reduce the administrative workload for both the CFDA and other relevant enterprises. Under the restructuring, five specific responsibilities have devolved from the central government to the provincial food and drug supervision and management departments. This includes re-registration of drugs and the supplementary applications for unchanged intrinsic quality medicines.

With sweeping changes already implemented and more in progress, the implications cannot be understated for EU SMEs operating in the Chinese pharmaceutical industry. It is certain that in the current environment of rapid change, businesses – particularly foreign enterprises – need to constantly follow and be informed of the latest developments.

At present, a number of laws are undergoing revision, and the CFDA announced in January 2014 that the revision of the Drug Administration Law has been included in the latest legislative plan of the Standing Committee of the People's Congress, and the CFDA is seeking public opinion on this revision at present. In February 2014, CFDA drafted the Measures of the Administration of Drug Registration (Amendment Bill) and published it on State Council's legislative affairs office website (www.chinalaw.gov.cn) to solicit public views on the amendment.

How to determine classification of a pharmaceutical product

The Chinese registration system for pharmaceutical products is divided into six classes. The classification system determines documentation and study requirements for pharmaceutical products, including whether or not clinical trials are required.

Classification of pharmaceutical products for registration		
Class	**Classification**	
1	**Pharmaceutical products (pending approval in all countries)**	
	1.1	Pharmaceutical products produced by synthetic or semi-synthetic methods
	1.2	Pharmaceutical products with effective monomers extracted from a natural resource or by fermentation
	1.3	Pharmaceutical products that are optical isomers produced by separation or synthesis from a known pharmaceutical product
	1.4	Pharmaceutical products transformed from a marketed product with multi-components and containing fewer components of that product
	1.5	New compounds
	1.6	New indications (not approved domestically or overseas) for a pharmaceutical product marketed in China
2	**Pharmaceutical products with a changed administration route (pending approval in all countries)**	
3	**Pharmaceutical products new to the Chinese market (approved in other countries)**	
	3.1	Pharmaceutical products and the raw medicinal materials that have been approved in any country, or products with changed dosage form but no change in administration route
	3.2	Compound products or changed dosage form with no change in administration route (approved in other countries)
	3.3	Pharmaceutical products with a change in administration route (approved in other countries)
	3.4	Pharmaceutical products marketed in China with new indications (approved in other countries)
4	**Pharmaceutical products with a change of their acid radical or base (or metal elements) but no change of pharmacology effects**	
5	**Pharmaceutical products marketed in China with a change in dosage form but no change in drug administration route**	
6	**Pharmaceutical substances and products included in Chinese national drug standards, such as Chinese pharmacopoeia or pharmaceutical registered standards**	

Note: For biological products and TCM, there are different classification systems

To illustrate the classification system, newly developed pharmaceutical products not approved for market (in any country) at the time of application should follow the requirements for class 1 pharmaceuticals. In addition, class 1 pharmaceuticals should, as a minimum, have entered phase II clinical trials (refer to section 4 of this guideline, "Clinical Study") when applying for Chinese pharmaceutical registration.

Imported pharmaceutical products already approved in the country of origin but not yet introduced to the Chinese market should follow the requirements for class 3 pharmaceuticals when submitting an application. The applicant can submit all materials using ICH's[1] common technical document (CTD) format; however, the comprehensive introduction section of the application is required to follow the Chinese requirements as outlined by the CFDA.

All imported pharmaceutical products are subject to the documentation requirements as described under classes 1 or 3.

The documentation requirements of the CFDA can be divided into four different modules, including the comprehensive introduction of the manufacturer, pharmaceutical study materials, pharmacology and toxicology, and clinical study Overall, the four modules identify 32 items for documentation (see section 2, "Application", later in this guideline).

Once the appropriate classification has been determined for the imported pharmaceutical product, the manufacturer can verify the necessary documentation requirements to support the application.

[1] International Conference on Harmonisation of Technical Requirements of Pharmaceuticals for Human Use.

How to apply for pharmaceutical registration?

Overall, the process can be divided into five steps:

1. **Appointing agent** – applicant must be a legal Chinese entity
2. **Application** – application and preparing supporting documentation covering the four modules indicated according to pharmaceutical classification
3. **Standards and testing** – compliance testing at a designated laboratory in China
4. **Clinical study** – depending on approval and classification, a clinical study may be required
5. **Registration of pharmaceutical product** – after completing the clinical study, the application should be resubmitted to include the findings of the study

1. Appointing agent

According to the regulation on drug registration, an application for pharmaceutical product registration can be carried out only by a Chinese legal entity. Overseas manufacturers of pharmaceutical products without legal representation in China are required to apply for product registration through an agent. In this case, the manufacturer is required to issue a power of attorney to the agent.

The agent will play an important role in the application process, and careful consideration should be made when selecting an agent. Important selection criteria should include the agent's experience in dealing with regulatory affairs, and so on.

2. Application

The application for pharmaceutical registration requires comprehensive supporting documentation according to the product classification. The following table summarises the documentation requirements; for convenience, they are categorised into four modules: introducing the pharmaceutical product, the study material, the pharmacology and toxicology study material, and the clinical study material. The table contains 32 items in total.

The documentation requirements are determined according to the classification of the pharmaceutical product. Annex 1 is a table indicating the various documentation requirements according to the classification of the product.

Once the application has been submitted to the CFDA's receiving office, it will be examined for consistency. Within five working days, the applicant will be informed whether or not the application was accepted.

Applicants should bear in mind that only applications submitted together with all supporting documentation will be accepted by the CFDA. Applications that are missing parts of the supporting documentation will be rejected, and unless explicitly requested, the CFDA will not accept missing documentation after the application has been received.

Once the application has been accepted by the CFDA, a testing laboratory notice will be issued and the application can proceed with product testing at a designated laboratory.

Documentation requirements		
Module 1: comprehensive introduction		
	Required item	Description
1	Name of pharmaceutical product	International non-proprietary name (INN) or generic name, chemical name, including chemical structure, molecular weight and formula. For new pharmaceutical products, the rationale of nomenclature should be provided.
2	Official documentation	• Business licence of the applicant • Manufacturing licence • Copy of GMP certificate or other compliance documents • Patent information and declaration of non-infringement • Documentation for pharmaceutical substances used, pharmaceutical standards, test reports, and business licences of suppliers, etc. • Legal documentation on packaging materials and containers in direct contact with the product (e.g. DMF[2] coding number or CEP certificate[3])
3	Purpose and rationale of the product research	Description of the purpose for developing the product and the requirements that it meets in China as well as other countries
4	Summary and results of R&D findings	A summary of the major outcomes of the study and an overview of the drug safety, efficacy and quality control
5	Instructions for use and relevant literature	Package insert sheet with directions for use
6	Package and label	Examples of label and packaging of the product (in Chinese and original language)
Module 2: pharmaceutical study materials		
7	Comprehensive introduction of the pharmaceutical study	Information regarding manufacturing process, administration method, formula development, identification of chemical structure, quality study and quality standards applied, stability study and any other related literature
8	Manufacturing process of substances and products, including literature	Detailed introduction to the manufacturing process of the pharmaceutical substances, the formula and the processing of products. Information on the process flow chart, chemical reaction information, reaction conditions, etc.

[2] Drug master file.
[3] Certificate of suitability.

9	Literature on chemical structure, components study and other references	
10	Quality study	Study material related to quality validation, including physical and chemical properties, purity test, dissolution test, methodology validation, etc.
11	Quality standards	Quality standards should be consistent with current versions of Chinese pharmacopoeia using its terminology and metrology as a minimum requirement
12	Test report	The test report carried out by the manufacturer
13	Information on testing of drug substance and excipients, with the standard/specifications and testing reports	
14	Stability study	The study data should include influential factors affecting the product and the drugs that have direct contact with packaging and containers
15	Quality specification of packaging materials and containers in direct contact with the product	
Module 3: pharmacology & toxicology study		
16	Comprehensive introduction to pharmacology and toxicology study	Information on the pharmacology and toxicology study, including pharmacodynamics, pharmaceutical action mechanism, general pharmacology, toxicology, pharmacokinetics, etc.
17	Major pharmacodynamics study	
18	General pharmacology study	
19	Acute toxicity testing	
20	Long-term toxicity testing	
21	Safety testing	Sensitivity (local, system and photo toxicity), haemolysis and topical (vessels, skin, etc.) irritation study, etc.
22	Component interaction	Effects of components in combination, toxicity, pharmacodynamics interaction
23	Mutagenicity study	
24	Reproduction study	
25	Carcinogenic study	
26	Drug dependence study	
27	Non-clinical pharmacokinetic study	All the information of the pharmacokinetic study by vitro and vivo in animal (absorption, metabolism, distribution and discretion)

Module 4: clinical study		
28	Comprehensive introduction to the clinical study conducted in China and other countries	
29	Clinical study plan and trial protocol	Detailed description of the intended indications, administration and dosage, etc. Supporting data and summary of the critical assessment of non-clinical and clinical data related to the potential risks and clinical benefits
30	The information brochure for clinical investigators	Information comprised of clinical study materials gained and non-clinical study information abstracts to help investigators and related staff understand the testing drug and clinical protocol
31	Patient relationship and ethics	Sample of patient consent forms and the clearance document of the ethical committee
32	Clinical study report	Copy of the full report

** All information should be provided in Chinese and original language*
** Source: *Measures of the Administration of Drug Registration*

3. Standards and testing

The Chinese National Institute for Food & Drug Control (NIFDC) will carry out the pharmaceutical registration test or delegate testing to a provincial drug quality control institute.

For drug registration testing, the applicant needs to prepare samples from three consecutive batches of the product and send them to the laboratory with a testing notice issued by the CFDA.

The applicant will need to fill in the test application form available on the NIFDC website: www.nicpbp.org.cn

The sample size will depend on applicable product standards, which will also describe the various items that need testing. In general, the test sample should be triple the amount of test items listed in the standard.

The test laboratory will undertake the testing based on product standards submitted with the application, or according to the Chinese national drug standards if these are listed in the application. The testing laboratory may also verify product quality standards. Revisions may be required to change some testing conditions, such as temperature or reagent flow rates.

The Chinese pharmaceutical standards system is independent from the national GB standards and follows the provisions of the Chinese Pharmaceutical Law.

The Chinese national standards for pharmaceutical products include two types of standards: Chinese pharmacopoeia and registered standards not listed in the pharmacopoeia. The Chinese pharmacopoeia can be purchased from the Chinese Pharmacopoeia Commission or its distributors.

Registered pharmaceutical products can also have registered standards. The registered standards should meet all the general principles of the Chinese pharmacopoeia: the format of its monograph, including the terminology and metrology. Most importantly, the registered standard should, as a minimum, meet the general safety and quality requirements of the Chinese pharmacopoeia standards.

The CFDA advises that testing will take up to 85 days to conclude, and the testing report will be sent to the CFDA's drug evaluation centre. One copy will be given to the applicant.

The designated test laboratories follow central pricing guidelines. The price list can be accessed on the CFDA website (available only in Chinese).

4. Clinical study

The Center for Drug Evaluation (CDE) will carry out a technical review of the test report. The full documentation usually takes from 40 to 160 days to complete, depending on the product. The review report will be sent to the CFDA with a recommendation as to whether the product is subject to a clinical trial or bioequivalence study in China. Further information can be found in the Measures of the Administration of Drug Registration, which outlines the requirements for clinical studies.

If the CDE deems that no clinical study is needed, the application will enter the final registration phase.

In sum, the clinical study can be divided into four phases; however, it is beyond this document to give a comprehensive introduction to clinical trials in China. Generally, phase I of the study needs between 20–30 subjects. Phase II is approximately 200 subjects. Phase III requires 300 subjects, and phase IV is conducted as a post-marketing study investigating around 2,000 subjects.

For class 3 pharmaceutical products, a study with 100 pairs of subjects is required. For a bioequivalence study, generally 18–24 subjects are needed.

Once the applicant receives approval for the clinical study, the applicant is free to choose the hospitals where the clinical study will be conducted. The CFDA website has a list of designated clinical research hospitals or medical institutions. It is a requirement that the clinical study be conducted at a minimum of two different hospitals.

The clinical study should be conducted in compliance with good clinical practice (GCP). All the pharmaceutical products used for the clinical study need to be tested, either self-testing by the manufacturer or contracted to a designated testing laboratory coordinated by the NIFDC.

After completing the clinical study, the clinical study plan, trial protocol, the approval documents from the ethical committee – together with patient consent forms and study report – will form part of the drug registration application.

It is difficult to make general statements about the timeframe for a Chinese clinical trial; this depends on availability of subjects, nature of disease, schedule of the hospital, and so on.

5. Registration of pharmaceutical product

After completing the clinical study and pharmaceutical registration test, the applicant fills in the drug registration form again and submits all documentation to the CFDA. The CDE will then review and evaluate all the submitted information. In some cases, the Center will involve external experts in the evaluation of the pharmaceutical product.

Once the CDE has passed final judgment, the file is transferred to the CFDA for final approval. It is ultimately the CFDA that make an administrative decision to grant or deny certification of the product.

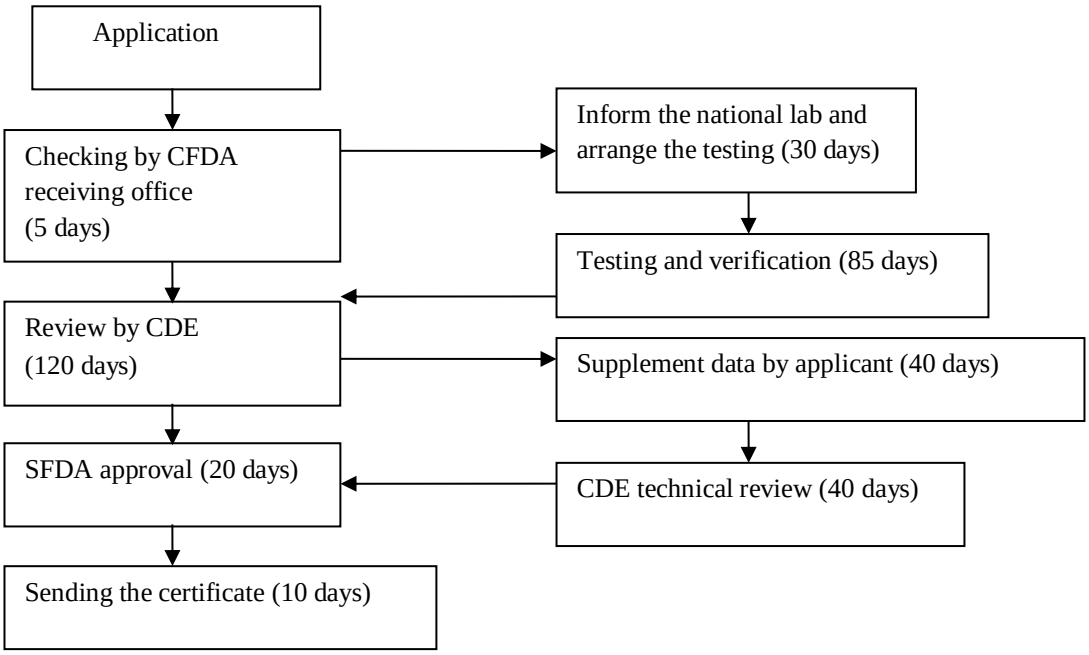
If the application is not approved, the applicant can apply for re-evaluation within 60 days.

The pharmaceutical registration certificate is valid for five years, and re-registration should begin at least six months prior to the certificate expiration. Re-registration should be submitted with all information of post-approval assessments in terms of safety, efficiency and quality of the product done or collected within the five-year validity period.

In addition to the testing fee for the pharmaceutical registration test and expenses for clinical trials, the drug registration fee amounts to CNY 45,300[4], which is paid directly to the CFDA.

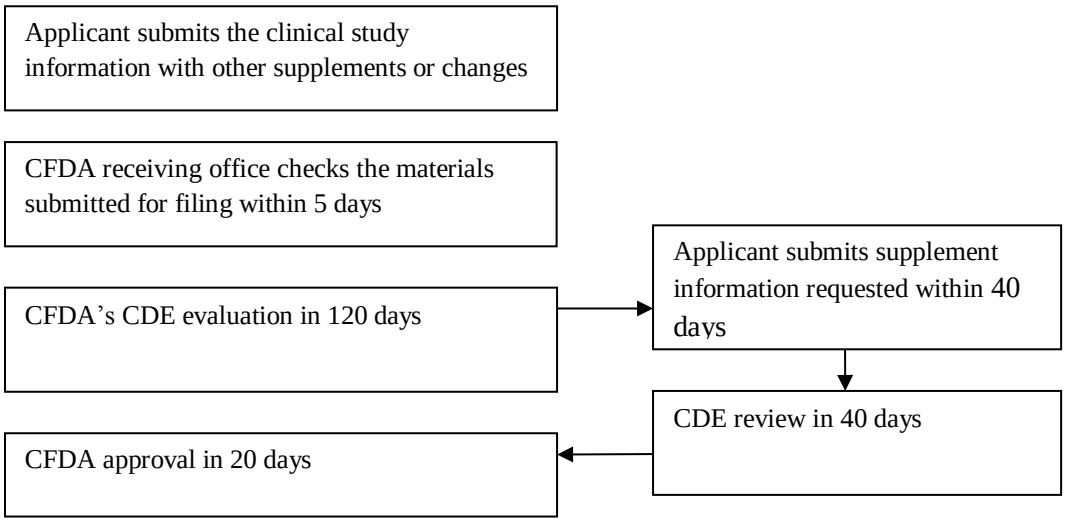
Below is the process flow chart for drug registration with time schedule:

Imported drug registration process flow chart (no clinical study)*



[4] Currency conversion as of 16th May 2014: EUR 1 = CNY 8.5440 (Bank of China).

Imported drug registration process flow (after clinical study)



Biological products registration

Biological products cover therapeutic and preventive biological products for registration purposes in China. Each of these has a different classification system and information requirements for registration. More details for each are provided as follows:

I. Therapeutic biological products

Classification of therapeutic biological products for registration	
Class	Classification
1	Biological products not yet marketed in China or overseas
2	Mono-clonal antibody
3	Gene therapy, somatic cell therapy as well as the preparations
4	Allergen products
5	Multi-component products with bioactivity extracted from or by fermentation from human and/or animal tissues and/or body fluid
6	A new combination product made from already marketed biological product(s)
7	A product that is marketed already overseas but not yet marketed in China
8	Some strains used for preparing micro-ecological products not yet approved
9	Products that do not have the exact structure of products already marketed and not yet marketed in China or overseas (including amino acid locus mutation/absence, modification caused by a different expression system, deletion, changed interpretation, as well as chemical modifications of the product)
10	Products with a method of preparation different from one already marketed (such as use of different expression system and host cells)
11	Products are manufactured for the first time with DNA recombination technology (such as using recombination technology to replace the synthesis technology, tissue extraction or fermentation technology)
12	Products transformed from non-injection into injection, or topical use into systemic use, and not yet marketed in China or overseas
13	Marketed products with a change in dosage form but no change in route of administration
14	Products with a change in route of administration (excluding the above category 12)
15	Biological products included in national standards

For the application of preparations not yet marketed in China or overseas, information shall be submitted in accordance with registration class 1.

For all products new to the Chinese market (approved in other countries), information shall be submitted in accordance with registration class 7, for all products already in the Chinese market, information shall be submitted in accordance with registration class 15.

Documentation requirements from the CFDA can be divided into five modules: comprehensive introduction of the manufacturer, pharmaceutical study materials, pharmacology and toxicology, clinical testing materials, and others. The table contains 38 items in total.

Information requirements for therapeutic biological products registration	
Class	**Module 1: comprehensive introduction**
1	Name of the drug
2	Certified documents
3	Objectives and basis for the application
4	Summary and evaluation of the main research results
5	Sample draft of insert sheet, notes to the draft, and literature
6	Sample design for packing, labelling
Class	**Module 2: pharmaceutical study materials**
7	Summary of pharmaceutical study information
8	Research information of the raw material used for production: • Research information about the sourcing, collection, and quality control of the animal or plant tissues or cells, unprocessed blood plasma • Research information about the sourcing, collection (or selection) process, and determining of cells used for production • Information about the establishment, determination, and storage of the strains banks, as well as the stability of transfer of culture • Research information about the sourcing, quality control of other raw materials used for production
9	Research information about the production process of the raw materials or unprocessed fluids
10	Research information of the formula and process of the preparations, source and quality standards of the supplements, as well as relevant literature

11	Information from experiments and literature on the quality study of the products, including the preparing and standardising of the standard material or controls, as well as the comparison information with similar products already marketed in China or overseas
12	Record of manufacturing and testing of the sample products to be used in the clinical study
13	Draft of the manufacturing and test standards, with notes to the draft and verification information of the test method
14	Preliminary research information about stability
15	Basis for selection and quality standards of immediate packing material and container
Class Module 3: pharmacology and toxicology study	
16	Summary of the pharmacology and toxicology study information
17	Information from experiments and literature on pharmacodynamics
18	Information from experiments and literature on a regular pharmacology study
19	Information from experiments and literature on acute toxicity
20	Information from experiments and literature on long-term toxicity
21	Information from experiments and literature on animal pharmacokinetics
22	Experimental data information and literature on mutations test
23	Experimental data information and literature on reproductive toxicity
24	Experimental data information and literature on carcinogenicity test
25	Research information and literature on immunotoxicity and/or immunogenicity
26	Information on experiments and literature from major special safety tests related to topical and systemic use of the drug, such as hemolysis and topical (blood vessel, skin, mucous membrane, endometrium, tunica and muscle) irritation
27	Information on experiments and literature on the effectiveness, toxicity and pharmacokinetics caused by the interactions between multiple components in the combination products
28	Information on experiments and literature on drug dependence
Module 4: clinical study	
29	Summary of clinical study in China and overseas
30	Clinical study plan and protocol
31	Investigator's brochure
32	Sample draft of informed consent form, approval of ethics committee
33	Summary report of the clinical study

Module 5: Others	
34	Brief summary of the pre-clinical study
35	Experiments and study information and summary of the production process improvement, quality perfection, pharmacology and toxicology study and other works conducted during the clinical study
36	Amendments and basis to amend of the approved manufacturing and testing standards
37	Research and study information of the stability test
38	Manufacturing and testing records of three consecutive batches of trial products
* All information should be provided in Chinese and original language ** Source: *Measures of the Administration of Drug Registration*	

Clinical study for therapeutic biological products registration

1. A clinical trial should be conducted for the application of new drug.
2. The number of participants tested for clinical trials should meet the statistical requirements and minimal case requirements.
3. The minimum test cases requirements for clinical trials are: phase I: 20–30, phase II: 100, phase III: 300.
4. Clinical trials for products under registration classes 1–12 should be conducted in accordance with requirements for new drugs.
5. Only a phase III clinical trial is typically required for products under registration classes 13–15.
6. For the renovated sustained released preparation, a comparative study of human pharmacokinetic study and clinical trials shall be conducted.

II. Preventive biological products

Classification of preventive biological products for registration	
Class	**Classification**
1	Vaccine not yet marketed in China or overseas
2	DNA vaccine
3	A vaccine already marketed with new adjuvant; change of carrier of combined vaccine
4	Non-purified vaccine, or full cell vaccine (bacteria, virus) changed into purified vaccine, or combined vaccine
5	Vaccine with strains not yet approved in China (except for vaccine for influenza, vaccine for leptospirosis and others)
6	Vaccine that has already been marketed overseas but not yet in China
7	Combined vaccine prepared with a vaccine already marketed in China
8	Re-combination vaccine with protective antigen spectrum that is different from a marketed vaccine
9	Vaccine manufactured with a change from other approved expressions or other approved cellular stroma; vaccines using a new manufacturing process that has proven to improve the safety and effectiveness of the vaccine based on data collected in the laboratory
10	Vaccine with the change from a de-activator (method of deactivation) or de-toxicitor (method of de-toxicity)
11	Vaccine with a change in the route of administration
12	Vaccine marketed in China with a change in dosage form but no change in route of administration
13	Vaccine with changes of immunity dosage or an immunity procedure
14	Vaccine with expanded population group of users (e.g. increasing age group)
15	Vaccine included in national standards

Note: Application information shall be submitted in accordance with the registration application information items. For application of vaccines not yet marketed in China or overseas, information shall be submitted in accordance with registration class 1. For all vaccines new to the Chinese market (approved in other countries), the information shall be submitted in accordance with registration class 6. For all vaccines already in the Chinese market, information shall be submitted in accordance with registration class 15.

Information requirements for preventative biological products registration	
1	Comprehensive introduction • Name of the new products • Certified documents • Objective and basis for the application • Sample draft of the insert sheet, notes to the draft and literature • Sample design of packing and labelling
2	Research information summary and the evaluation information
3	Research information on the production bacterial and toxicity strains • Source and characteristics: including the source of the production bacterial and toxicity strains, research information or certified documents to show the bacterial and toxicity strains can be used for production, history of the product including history of separation, determination and de-toxicity, characteristic, research information on the adaptability to cellular stroma, infective titer, antigenocity, immuno-genecity, toxic (or toxicity) • Batches of the strains: relevant information on initial batch of the production bacterial and toxicity strains, primary generation batch, information of the establishment of production batch bank (including generation numbers, the preparation, storage of sub-batch of production strains, test report of each batch of production bacterial and toxicity strains, items to be tested including exogenesis factors, determination test, characteristic, infective titer, antigenocity, immunocity). For a strain of primary generation, the gene sequence should be determined • Research data on the stability of bacterial and toxicity strains passage: determining the limitation of the last generation number to be used. For items to be tested, refer to the test items of batches of strains • Test report of batches of bacterial and toxicity strains used for production from NIFDC
4	Research information of the cellular stroma for production • Source and characteristic: source of cellular stroma used for production, certified documents and research information to show that the cellular stroma can be used for production, its history (including history of establishment of cells system, determining, and history of transfer of culture), biological characteristics, exogenesis factors test, analysis of karyotype, tumorigencity test and other studies • Cell bank: including information on the establishment of production cellular stroma initial cell bank, primary cell bank, production cell bank (including the generation number, preparation, storage and administration of the various production cell banks, comprehensive tests of cell banks). Items to be tested include biological characteristic, karyon type analysis and exogenesis factors inspection • Stability of transfer of culture: determining the limitation of last generation number to be used. For items to be tested, refer to items to be tested of the cell bank, with addition of tumorigenicity • NIFDC test report of the production cells bank for cellular stroma used for manufacturing • Source and quality standards of culture fluid, addictive and others; in the event that material sourced from cows is used, relevant information should be provided in accordance with requirements of CFDA

5	Research information of production process and technology • Research of the production process of original fluid of the vaccine: the main technical parameters to optimise the production process, including inoculation quantity of bacteria (or virus), culture conditions, fermentation condition, de-activity and crack process conditions, extraction and purifying of the bioactive material, removal of the material potentially toxic to humans, activation, coupling and combination technology of antigen and carrier for the combined vaccine, research information of the percentage of various bioactive components, compatibility of antigen, etc.; summary of the materials input, output of various intermediary products and the quality during the production process, finished product output and quality should be provided • Formula and production process of the preparations, and the basis to determine shall be provided; source and quality standards of the supplements shall be provided
6	Research information of the quality of the product: after the determination of production process, information should be determined using statistical methods, based on test results of multi batches of the pilot product • Quality standards and test results of the products, including quality standards and test results of the each single component of the combined vaccine • Research and verification information of the test method • Analysis information of product antigencity, product immunocity and protectiveness of the animal test • For any potential human toxic material introduced during the production process, the research information about the removal effect of process should be provided and the standard to control the material within the limit should be established; the basis for the standards should also be provided • Research information of animal hypersensitivity test • Comparison information with a similar product • Measuring of antigen components, contents, molecular weight, purity; specificity determination; and measure and the test of the content (or residual) of the non-effective component • Information on the evaluation of tests on animal safety • For the vaccine manufactured with the use of DNA recombination technology, requirements for therapeutic biological products shall apply
7	Draft of manufacturing and testing standards drafted in accordance with relevant regulations, attached with the notes on how each items were drafted, and the relevant literature
8	Record of the manufacturing and testing of a sample product to be used for in the clinical study
9	Preliminary stability test information
10	Quality certificate of the animal used for production, research and test
11	The clinical study plan and study protocol
12	Summary of the pre-clinical study
13	Summary information of the relevant clinical studies in China and overseas
14	Summary of clinical study report including sample of informed consent form, approval from the ethics committee

15	Summary of work, experiment and study information on the improvement of the production technology and the perfection of quality standards during the clinical study
16	Stability research information to determine the storage and validity period of the vaccine
17	Amendments and the basis to amend the approved manufacturing and test standards
18	Record of production and testing of three consecutive batches of trial products
* All information should be provided in Chinese and original language ** Source: *Measures of the Administration of Drug Registration*	

Clinical study information

1. Number of participants (subject) for clinical trials should meet statistical requirements and minimum cases requirements. Minimal cases include both a trial group and control group.
2. Minimal cases requirement for clinical trials are: phase I: 23–30, phase II: 300, phase III: 500.
3. For vaccines under registration classes 1–9 and 14, the clinical trials should be conducted in accordance with the requirement for new drugs.
4. For vaccines under registration class 10, if the research information provided shows there is no change in the safety and effectiveness of the vaccine after the deactivation or de-toxicity of the vaccine, a normal clinical trial is not required.
5. For vaccines under registration class 2, a clinical trial should typically be conducted in accordance with requirements for a new drug. However, phase I clinical trials may not be required if the route of administration has simply changed from injections into non-injections.
6. Only a phase III clinical trial is required for vaccines under registration classes 12 and 15.
7. For vaccines under registration class 13, a phase I clinical trial may not be needed where the immunity procedure is changed.
8. For preventive products used in infants, in principle, the sequence of phase I clinical trials should be adults first, then children and then infants.
9. Each phase of clinical trials should be conducted after the completion of proviso phase in accordance with the prescribed immunity procedures.
10. For the first application of a vaccine to be marketed in China, an epidemiological test for the protective properties should be performed.

Annex 1: items required for submission for pharmaceutical products registration

As mentioned on page 4, the documentation requirements of the CFDA can be divided into four modules: comprehensive introduction of the manufacturer, pharmaceutical study materials, pharmacology and toxicology, and clinical study. Overall, the four modules identify 32 items for documentation (see section 2, "Application," later in this guideline).

Module	Item	Registration classification and requirements					
		1	**2**	**3**	**4**	**5**	**6**
Comprehensive introduction	**1**	+	+	+	+	+	+
	2	+	+	+	+	+	+
	3	+	+	+	+	+	+
	4	+	+	+	+	+	+
	5	+	+	+	+	+	+
	6	+	+	+	+	+	+
Pharmaceutical study	**7**	+	+	+	+	+	+
	8	+	*4	+	+	*4	*4
	9	+	+	+	+	+	+
	10	+	+	+	+	+	+
	11	+	+	+	+	+	+
	12	+	+	+	+	+	+
	13	+	+	+	+	+	+
	14	+	+	+	+	+	+
	15	+	+	+	+	+	+
Pharmacology and toxicology study	**16**	+	+	+	+	+	+
	17	+	*14	±	*16	−	−
	18	+	*14	±	*16	−	−

	19	+	*14	**±**	*16	–	–
	20	+	*14	**±**	*16	–	–
	21	***17**	*17	***17**	*17	*17	*17
	22	***11**	–	–	–	–	–
	23	+	±	**±**	±	–	–
	24	+	±	**±**	±	–	–
	25	***6**	–	***6**	*6	–	–
	26	***7**	–	–	–	–	–
	27	+	*18	***18**	+	*18	–
Clinical study	**28**	+	+	**+**	+	+	+
	29	+	+	**+**	+	+	△
	30	+	+	**+**	+	+	△
	31	+	+	**+**	+	+	△
	32	+	+	**+**	+	+	△

Notes:

"+" means that the materials must be submitted.

"±"means that the test data can be replaced with a literature review.

"–"means that the manufacturer is not required to submit the material.

"*" refers to the notes attached to the Measures of the Administration of Drug Registration, e.g. *6 refers to note 6 in the measurements.

"△ " refers to specific notes related to clinical study requirements described in Measures of the Administration of Drug Registration.

Literature includes pharmacology and toxicology study such as pharmacodynamics, drug actions, mechanisms, general pharmacology, toxicology and pharmacokinetics.

Further information can be found on the CFDA website.

Annex 2: items required for the submission of therapeutic biological products registration

1. Application information items for therapeutic biological products (items 1–15, 29–38)

Information category	Items	Registration category and information item requirement														
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Summary information	1	+	+	Refer to guiding principle	Refer to guiding principle	+	+	+	+	+	+	+	+	+	+	+
	2	+	+			+	+	+	+	+	+	+	+	+	+	+
	3	+	+			+	+	+	+	+	+	+	+	+	+	+
	4	+	+			+	+	+	+	+	+	+	+	+	+	+
	5	+	+			+	+	+	+	+	+	+	+	+	+	+
	6	+	+			+	+	+	+	+	+	+	+	+	+	+
Pharmaceutical information	7	+	+			+	+	+	+	+	+	+	–	+	–	+
	8	+	+			+	–	+	+	+	+	+	–	–	–	+
	9	+	+			+	–	+	+	+	+	+	–	–	–	+
	10	+	+			+	+	+	+	+	+	+	–	+	–	+
	11	+	+			+	+	+	+	+	+	+	–	+	–	+
	12	+	+			+	+	+	+	+	+	+	–	+	–	+
	13	+	+			+	+	+	+	+	+	+	–	+	–	+
	14	+	+			+	+	+	+	+	+	+	–	+	–	+
	15	+	+			+	+	+	+	+	+	+	–	+	–	+
Clinical information	29	+	+			+	+	+	+	+	+	+	+	+	+	+
	30	+	+			+	+	+	+	+	+	+	+	+	+	+
	31	+	+			+	+	+	+	+	+	+	+	+	+	+
	32	+	+			+	+	+	+	+	+	+	+	+	+	+
	33	+	+			+	+	+	+	+	+	+	+	+	+	+
Others	34	+	+			+	+	+	+	+	+	+	+	+	+	+
	35	+	+			+	+	+	+	+	+	+	+	+	+	+
	36	+	+			+	+	+	+	+	+	+	–	+	–	+
	37	+	+			+	+	+	+	+	+	+	–	+	–	+
	38	+	+			+	+	+	+	+	+	+	–	+	–	+

Notes: "+" denotes information must be submitted; "–" denotes information may be exempted from submission.

2. Application information items for pharmacology and toxicology information for therapeutic biological products (items 14–29)

Information categories	Information items	Category and information item requirement														
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Pharmacology and toxicology information	16	+	+	Refer to guiding principle	Refer to guiding principle	+	+	+	+	+	+	+	+	+	+	+
	17	+	+			+	+	+	+	+	+	+	+	+	+	+
	18	+	+			+	+	+	+	+	+	+	+	+	+	+
	19	+	+			+	+	+	+	+	+	+	+	+	+	±
	20	+	+			+	+	+	+	+	+	+	+	+	+	+
	21	+	+			±	±	±	–	+	±	+	+	±	+	±
	22	±	±			±	±	±	–	±	±	±	±	–	±	–
	23	±	±			±	±	±	–	±	±	±	±	–	±	–
	24	±	±			±	±	±	–	±	±	±	±	–	±	–
	25	+	+			+	+	+	–	+	+	+	+	–	+	±
	26	+	+			+	+	+	–	+	+	+	+	+	+	±
	27	–	–			–	+	–	–	–	–	–	–	–	–	–
	28	±	±			±	–	–	–	±	–	–	±	–	–	–

Notes: "+" denotes information must be submitted, "–" denotes information may be exempted from submission, "±" denotes information required or not required based on the particular case.

Annex 3: items required for submission for preventive biological products registration

Information item	Registration category and information item requirement														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
2	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
3	+	+	–	–	+	+	+	+	±	–	–	–	–	–	+
4	+	+	–	–	+	+	+	+	±	–	–	–	–	–	+

5(1)	+	+	+	+	+	+	+	+	+	+	–	–	–	–	+
5(2)	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+
6	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
7	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
8	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
9	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
10	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
11	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
12	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
13	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
14	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
15	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
16	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
17	+	+	+	+	+	+	+	+	+	+	+	+	+	+	±
18	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

Notes: "+" denotes information must be submitted, "–" denotes information may be exempted from submission, "±" denotes information required or not required based on the particular case.

Links to the Chinese administration webpages

1. Website: http://www.gov.cn/ldhd/2013-12/28/content_2556357.htm (in Chinese), Amending the Drug Administration Law of the People's Republic of China
2. Website: http://www.sfda.gov.cn/WS01/CL0371/76179.html, imported therapeutic biological products registration process
3. Website: http://www.sfda.gov.cn/WS01/CL0371/76180.html, imported preventive biological products registration process
4. Website: http://www.sfda.gov.cn/WS01/CL0025/ (in Chinese), imported drugs registration process
5. Website: http://eng.sfda.gov.cn/WS03/CL0768/ (in English), Measures of the Administration of Drug Registration
6. Website: http://www.sfda.gov.cn/WS01/CL0053/24529.html (in Chinese), therapeutic biological products and preventive biological products
7. Website: http://www.sfda.gov.cn/WS01/CL0778/96959.html (in Chinese), Measures of the Administration of Drug Registration (Revision)

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Contact the Centre at:

Room 910, Sunflower Tower
37 Maizidian West Street
Chaoyang District
Beijing, 100125

T: +86 10 8527 5300
F: +86 10 8527 5093

www.eusmecentre.org.cn
info@eusmecentre.org.cn

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