Importing pharmaceutical products to China

Imported pharmaceutical products need pre-market approval before entering the Chinese market

Imported drugs for human use are required to obtain pre-market approval from the Chinese State Food and Drug Administration (SFDA) before being placed on the Chinese market. This requirement applies to all drug products (medicines), including innovative drugs, generic or over-the-counter (OTC) drugs. In addition, a drug substance or active pharmaceutical ingredient (API) will also need pre-approval by the SFDA.

The definition of drugs in China covers chemical and biological products (vaccines, blood products and biotech products, etc.) and Traditional Chinese Medicine (TCM). Pharmaceutical products are commonly referred to as chemical drugs under Chinese legislation. The main focus of this guideline will be on imported chemical drugs for registration in China. For overall consistency, the term 'pharmaceutical products' will be used throughout this guideline.

Imported pharmaceutical products are subject to rules on drug registration which are based on the Chinese Drug Law and its implementation regulation. The "*Drug Administration Law of the People's Republic of China*" (2001) 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*" outlines the detailed technical requirements and procedure for application and approval.

The SFDA is the competent authority responsible for registering and handling application for imported pharmaceutical products. www.sfda.gov.cn

How to determine classification of a pharmaceutical product?

The Chinese registration system for pharmaceutical products is divided into 6 classes. The classification system determines the documentation and study requirements for the pharmaceutical product, such as if clinical trials are required or not.

Classification of pharmaceutical products for registration		
Class	**Classification**	
1	**Pharmaceutical products (pending market 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 which 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 market 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, and/or products with changed dosage form but no change to administration route
	3.2	Compound products and/or changed dosage form with no change of administration route which have been approved in other countries
	3.3	Pharmaceutical products with changed administration route which have been approved in other countries
	3.4	Pharmaceutical products marketed in China with new indications that have been 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 of dosage form but no change of drug administration route.	
6	Pharmaceutical substance and products that have been included into 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 that have not yet received market approval (in any country) at the time of application should follow the requirements for class I pharmaceuticals. In addition, Class I pharmaceuticals should, as a minimum, have entered phase II clinical trials (refer to section 4 of this guideline: *Clinical study*) at the time 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 of class III when submitting the application. The applicant can submit all materials using ICH's [1] Common Technical Document (CTD) format, however the comprehensive introduction part of the application needs to follow the Chinese requirements as outlined by the SFDA.

All imported pharmaceutical products are subject to the documentation requirements as described under classification I or III.

The documentation requirements of the SFDA can be divided into 4 different modules, including the comprehensive introduction of the manufacturer, pharmaceutical study materials, pharmacology and toxicology. Overall, the 4 modules identify 32 items for documentation (see section 2: *Application* later in this guideline).

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

How to apply for pharmaceutical registration?

Overall, the process can be divided into 5 steps:

1. **Appointing agent** – applicant must be a legal Chinese entity;
2. **Application** – application and preparing supporting documentation covering the 4 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 clinical study may be required;
5. **Registration of pharmaceutical product** – after completing the clinical study the application should be resubmitted including the information provided by the study.

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

1. Appointing agent

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

The agent will play an important part of the application process and careful considerations should be given when selecting an agent. The important selection criteria can be the agent's experience in dealing with regulatory affairs, etc.

2. Application

The application for pharmaceutical registration requires comprehensive supporting documentation according to the classification of the product. The table below summarises the documentation requirements and, for convenience, categorises them into 4 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. Annexed to this guideline is a table indicating the various documentation requirements according to the classification of the product.

Once the application has been submitted to the SFDA's receiving office it will be examined for consistency and the applicant will be informed if the application is accepted or not within 5 working days.

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

Once the application has been accepted by the SFDA, a testing laboratory notice will be issued and the application can proceed with testing the product 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	- The 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 the business licence 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 giving 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.
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	The 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.

[2] Drug Master File.
[3] Certificate of suitability.

13	Information on testing of drug substance and excipients, with the standard/specifications and testing reports.	
14	Stability study	The study data should include the study on influential factors affecting the product and the study on drugs with direct contact with packaging and containers.
15	Quality specification of packaging materials and containers in direct contact with the product.	
Module 3. Pharmacology and 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	The 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. The supporting data and the summary of the critical assessment of non-clinical and clinical data which is related to the potential risk and clinical benefit.
30	The information brochure for clinical investigators	A form of information compiling covering clinical study materials gained and non-clinical study information abstracts in order to help the investigators and related staff know 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 of Drug Quality Control on Pharmaceuticals and Biological Products (NIFDC) will carry on the pharmaceutical registration test or delegate the testing to a provincial drug quality control institute.

For the drug registration testing, the applicant needs to prepare samples from 3 consecutive batches of the production and send it to the laboratory with a testing notice issued by SFDA.

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 will 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 the product standards submitted with the application or according to the Chinese National Drug Standards if these have been listed in the application. The testing laboratory may also verify the 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, namely Chinese Pharmacopoeia and registered standards not listed in the Pharmacopoeia. Chinese pharmacopoeia can be bought 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, in 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 SFDA advises that the testing work will take up to 85 days to conclude and the testing report will be sent to the SFDA's Drug Evaluation Centre and one copy will be given to the applicant.

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

4. Clinical study

The Centre for Drug Evaluation will carry out a technical review of the test report and overall documentation which usually takes from 40 to 160 days to complete, depending on the product. The review report will be sent to the SFDA with recommendation on 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 Centre for Drug Evaluation deems that no clinical study is needed, the application will enter the final registration phase.

In summary, the clinical study can be divided into 4 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 to 30 subjects, phase II is approximately 200 subjects, phase III is 300 subjects, and phase IV is conducted as a post-marketing study investigating around 2000 subjects.

For class III 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 from a list of designated clinical research hospitals or medical institutions listed on the SFDA website. It is a requirement that the clinical study needs to 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 by 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 by the Ethical Committee, together with patient consent forms and study report will form part of the drug registration application.

It is difficult to give general statements about the timeframe for a Chinese clinical trial, as this will depend on availability of subjects, nature of disease, schedule of the hospital, etc.

5. Registration of pharmaceutical product

After completing the clinical study and pharmaceutical registration test, the applicant will need to fill in the drug registration form again and submit all documentation to the SFDA. The SFDA's Drug Evaluation Centre will review and evaluate all the submitted information. In some cases, the Drug Evaluation Centre will involve external experts in the evaluation of the pharmaceutical product.

Once the Drug Evaluation Centre has passed its final judgment, the file is transferred to the SFDA for final approval. It is ultimately the decision of the SFDA to make its administrative decision for granting certification of the product or not.

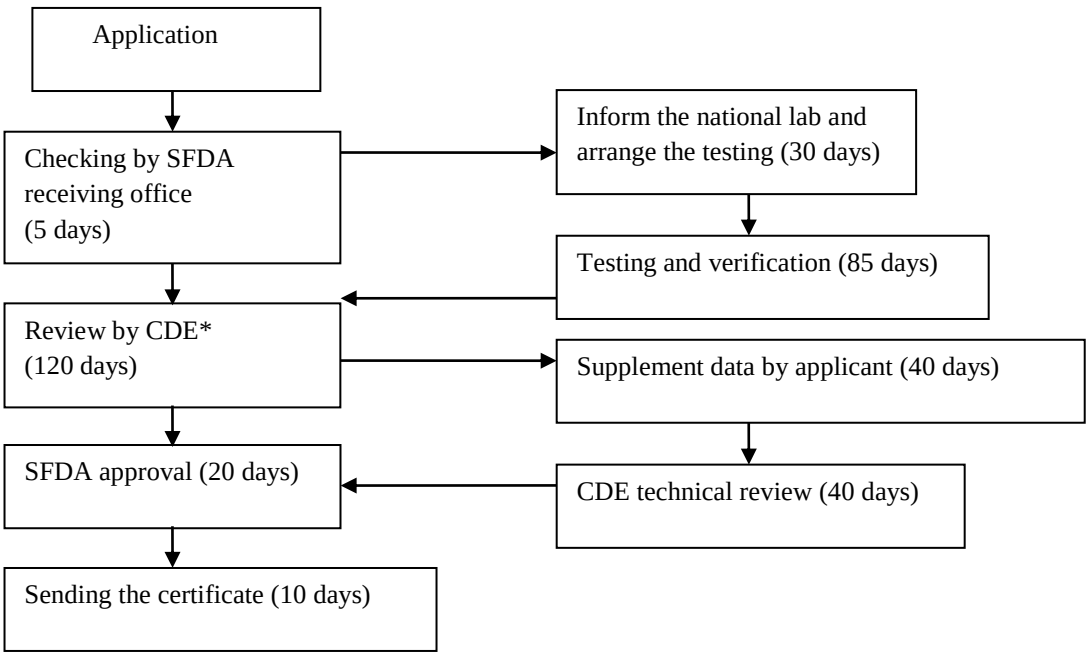
If the application is not approved, the applicant can apply for re-evaluation within 60 days.

The pharmaceutical registration certificate is valid for 5 years and re-registration should be applied for at least 6 months prior to the certificate expiring. Re-registration should be submitted with all information of post-approval assessments in terms of the safety, efficiency and quality of the product done or collected within the 5 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 (2011)[4] which is paid directly to the SFDA.

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

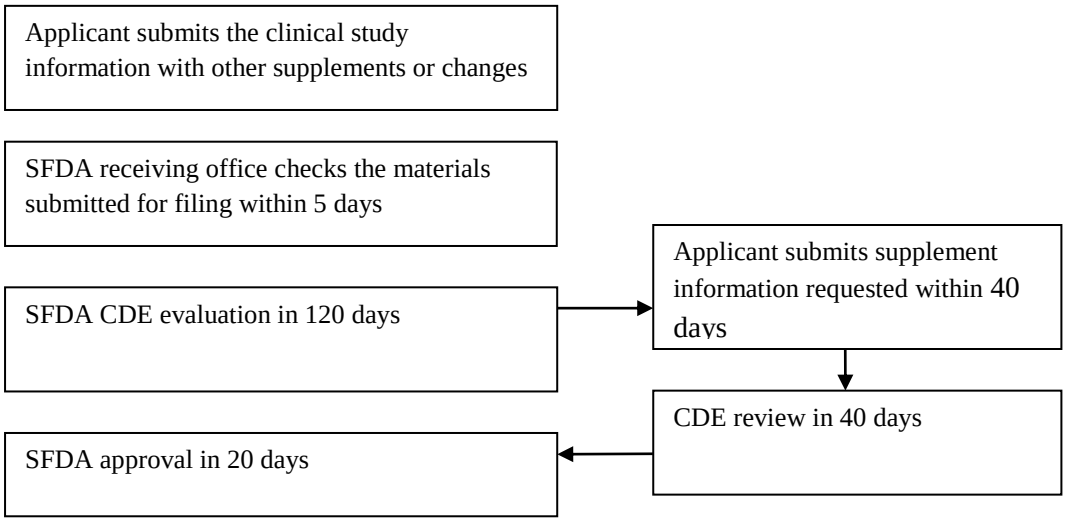
Imported drug registration process flow chart (no clinical study)



* CDE: Centre for Drug Evaluation

[4] Currency conversion as of August 12th 2011: EUR 1 = CNY 9.0866 (Bank of China).

Imported drug registration process flow (after clinical study)



Annex 1: Items required for submission

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:**

1.“＋”means that the materials must be submitted.

2.“±”means that the manufacturer can submit the original literature, no testing required.

3.“—”means that the manufacturer is not required to submit the material.

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

5.“Δ” refers to specific notes related to clinical study requirements described in “*Measures of the Administration of Drug Registration*”.

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

Further information can be found on the SFDA website.

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