

DRUG REGISTRATION REGULATION

Registration Categories and Application Information Items Requirements of Biological Products

Part I Therapeutic Biological Products

I Registration Categories

- 1) Biological products not yet marketed at domestic 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) New combination product made from the already marketed biological products.
- 7) A product that is marketed already overseas but not yet marketed domestic.
- 8) Some of the strains used for preparing of micro-ecological products not yet approved.
- 9) Products with not completely same structure with the already marketed products and not yet marketed at domestic 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 with the already marketed one, (such as use of different expression system, host cells).
- 11) Products first time made with DNA recombination technology (such as use of 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 at domestic or overseas.
- 13) The 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 admitted with National Standards.

II Application Information Items

A Summary information

- 1) Name of the drugs.
- 2) Certified Documents.
- 3) Objectives and basis for the application.
- 4) Summary and evaluation of main research results.
- 5) Sample draft of insert sheet, notes to the draft, and literature.
- 6) Sample design for packing, label.

B Pharmaceutical Study Information

- 7) Summary of Pharmaceutical Study Information.
- 8) Research information of the raw material used for production.
 - i) Research information about the sourcing, collection, and quality control of the animal or plant tissues or cells, unprocessed blood plasma.
 - ii) Research information about the sourcing, collection (or selection) process, and determining of cells used for production.
 - iii) Information about the establishment, determination, and storage of the strains banks, as well as the stability of transfer of culture.
 - iv) 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 the unprocessed fluids.
- 10) Research information of the formula and process of the preparations, source and quality standards of the supplementives, as well as the relevant literatures.
- 11) Experiment information and literature of the quality study of the products, including the preparing and standardizing of the Standard Material or Controls, as well as the comparison information with those similar product already marketed at domestic or overseas.
- 12) Record of manufacturing and testing of the sample products to be used for application of clinical study.
- 13) Draft of the manufacture and test standards, with notes to the draft and

verification information of the test method.

- 14) Preliminary research information about the stability.
- 15) Basis for selection and quality standards of immediate packing material and container.

C Pharmacology and Toxicology Study Information

- 16) Summary about the pharmacology and toxicology study information.
- 17) Experiments information and literature of pharmacodynamic.
- 18) Experiments information and literature of regular pharmacology study.
- 19) Experiments information and literature of acute toxicity.
- 20) Experiments information and literature of long term toxicity.
- 21) Experiments information and literature of animal pharmacokinetics.
- 22) Experimental data and literature of mutations test.
- 23) Experimental data and literature of reproductive toxicity.
- 24) Experimental data and literature of carcinogenicity test.
- 25) Research information and literature of immunotoxicity and / or immunogenicity.
- 26) Experiments information and literature on major special safety test information related to topical and systemic use of the drugs, such as hemolysis and topical (blood vessel, skin, mucous membrane, endometium, tunica and muscle) irritation.
- 27) Experiments information and literature of the efficacy, toxicity and pharmacokinetics caused by the interactions between multiple components in the combination products.
- 28) Experiment information and literature of drug dependence.

D Clinical Study Information

- 29) Summary of clinical study at domestic and overseas.
- 30) Clinical study plan and protocol.
- 31) Investigator's Brochure.
- 32) Sample draft of Informed Consent Form, approval of the ethics committee.
- 33) Summary report of the clinical study.

E Others

- 34) Brief summary of the pre-clinical study.
- 35) Experiments and study information and summary of the production process improvement, quality perfection, the 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 the 3 consecutive batches of trial products.

III Notes to the application information

- 1) Information Items 1-30 shall be submitted for application of clinical study. Items 1-6, 15 and 29-38 shall be submitted upon completion of clinical study. Items 1-6 and items 29-37 shall be submitted for application of New Drug Certificate.
- 2) Information Item 1, Name of the new drug, including International Nonproprietary Name, English name, China adopted name and its Chinese phonetics, molecular weight. The nomenclature of the drug should be explained for any new name.
- 3) Item 2, Certified Documents includes,
 - i) Copies of Certified Documents of lawful registration of the Applicant (business licenses), *Drug Manufacturing License* and change registration, *GMP Certificate*.
 - ii) Documents stating patent status and ownership or the biological products of application, or the formula used, process used, and letters of guarantee stating that no infringement upon the patent rights of others.
 - iii) Copy of *Approval of Clinical Study of New Drugs* should be provided for application of the production of new biological product.
 - iv) Copies of the *Drug Packing Material and Container Certificate* or *Import Drug Packing Material and Container Certificate* for the immediate packing material and container.
- 4) Information Item 3, objective and basis for the application, includes the current status and relevant literature of the research, marketing, and the relevant literature of the products, or the summary of production, the use of the products at domestic and overseas. Analysis of the renovation, and feasibility of the products.

- 5) Information Item 4, summary and evaluation of main research results, include the summary of the main research results of the products, and a comprehensive evaluation of the safety, efficacy, quality controllability of the products.
- 6) Information Item 5, sample draft of insert sheet, notes to the draft, and literature, includes the sample draft of the insert sheet drafted in accordance with the relevant regulations, notes to all the items of the draft of the insert sheet, relevant literature or the latest version of the insert sheet from the original manufactures in the original language and the translations.
- 7) For any production use of raw materials sourced from cows, relevant material required by SFDA should be provided.
- 8) For products extracted from human and /or animal tissues and body fluid, and / or for the re-combination products by expression of McAb and eukaryote, additional information for the verification of de-activation process of virus should be added.
- 9) 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, and basis for the standards should be provided.
- 10) Information item 11, information of quality study of the product, includes analysis of physical-chemical characteristic, determining of the structure, verification test, purity measuring, content measuring, and bioactivity measuring of the product. Additional research information on analysis of impurity should be provided for the purified products.
- 11) Safety research information (Information Items 19-28) may be exempted from the submission for the materials extracted from human tissues or body fluid, if the dosage does not exceed the physiologically tolerance limit and the biological products (excluding combination products) were processed not by special process technology, with no use of special menstruum.
- 12) During the pre-clinical study of the biological products, the correlated species of animal (refer to the animal where pharmacological activation of the tested drugs can be generated in vivo through the expression recipient and antigen epitope of animal) should be used for in vitro and / or in vivo tests. If some of the regular toxicology study, such as genetic toxicology, carcinogenicity, and hypersensitivity test are not applicable for biological products under the application, explanation should be provided and if necessary, other relevant study information and explanation should be provided.

- 13) Because of the diversity and complication of the biological products, so information should be provided with scientific and reasonable reference to the relevant guiding principle, taking the particular characteristic of the biological products, to meet the requirement of drugs evaluation during the application of a particular biological product.
- 14) The Applicant of an in vivo diagnosis biological product should proceed in accordance with the requirements for therapeutic biological products.

IV Requirement of the application information

A Table of Application Information Items for therapeutic biological products,
 (Information Items 1-15, 29-38)

INFORMATION	Category	Information Items	Registration Category and Information Item requirement																
			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15		
Summary Info	1		+	+	Refer to guiding principle	Refer to guiding principle	+	+	+	+	+	+	+	+	+	+	+		
	2		+	+			+	+	+	+	+	+	+	+	+	+	+	+	+
	3		+	+			+	+	+	+	+	+	+	+	+	+	+	+	+
	4		+	+			+	+	+	+	+	+	+	+	+	+	+	+	+
	5		+	+			+	+	+	+	+	+	+	+	+	+	+	+	+
	6		+	+			+	+	+	+	+	+	+	+	+	+	+	+	+
Pharmaceutical Info	7		+	+			+	+	+	+	+	+	+	+	-	+	-	+	
	8		+	+			+	+	+	+	+	+	+	+	-	-	-	+	
	9		+	+			+	+	+	+	+	+	+	+	-	-	-	+	
	10		+	+			+	+	+	+	+	+	+	+	-	+	-	+	
	11		+	+			+	+	+	+	+	+	+	+	-	+	-	+	
	12		+	+			+	+	+	+	+	+	+	+	-	+	-	+	
	13		+	+			+	+	+	+	+	+	+	+	-	+	-	+	
	14		+	+			+	+	+	+	+	+	+	+	-	+	-	+	
	15		+	+			+	+	+	+	+	+	+	+	-	+	-	+	
Clinical Info	29		+	+	+	+	+	+	+	+	+	+	+	+	+	+			
	30		+	+	+	+	+	+	+	+	+	+	+	+	+	+			
	31		+	+	+	+	+	+	+	+	+	+	+	+	+	+			
	32		+	+	+	+	+	+	+	+	+	+	+	+	+	+			

other	33	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
	34	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
	35	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
	36	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+
	37	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+
	38	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+

Notes:

1. + denote the information must be submitted,
2. - denote the information may be exempted from submission.

B Table of Application Information Items for pharmacology and toxicology information for therapeutic biological product (Information Items 14-29)

category	item	Registration 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:

1. + denote the information must be submitted,
2. - denote the information may be exempted,
3. ± denote the information required or not required based on the particular case.

C Notes for the Table of Application Information Items

- 1) For the products under Registration Categories 7, 10 and 15, comparison research shall be conducted to verify that the preparation process, quality research and bioactivity (including, if necessary, pharmacokinetic characteristic) of the products are basically the same with the already marketed products. Only one relevant animal is needed for toxicology test and study. Normally only one month of study is needed for long term toxicity test. Normal pharmacology study may be conducted during the long-term toxicity test. Comprehensive considerations shall be given for Pharmacodynamic study to be conducted based on the test results of the bioactivity during the quality research. If necessary, the pharmacology and toxicology study information compared with the marketed one, or other comparison information shall be provided, based on the complication of the molecular structure, the possibility of difference and how much the difference is between the product and the marketed one in pharmaceutical aspect, and characteristic of the indications. If there are sufficient evidence to verify the consistency between the product and the marketed one, the corresponding pharmacology and toxicology requirement may be applied for reduction or exemption.
- 2) For the products under Registration Category 2, during the designing of the pharmacology and toxicology tests, the followings shall be taken into

consideration

- i. When there is antibody combination information to indicate that the quadruman shall be the most correlated specie, for the uncoupled Mono-Clonal Antibody test, the animal of this specie shall be used to conduct the main pharmacology and pharmacokinetic study.
 - ii. For toxicology and pharmacokinetic study, the test should best be conducted on the animal experimental model with the same target antigen with human. If there is neither suitable animal experimental model nor animal with relevant antigen, and the cross-reaction test result with human tissue is negative, then toxicology study information may be exempted.
 - iii. Normally, animal toxicity with multi doses of drugs and regular inheritance toxicity test is not needed for Mono- Clonal Antibody (McAb).
 - iv. For the products to be repetitive or long term used with people at child bearing age, reproductive toxicity test should be conducted with the appropriate animal experimental model.
 - v. Immuno-toxicity study should focus on the potential toxicity reaction when combining the non-target tissues, such as the cross reaction with the human tissues / cells or the combination with non-target tissue. If there is a suitable experimental model, cross-reaction tests should be conducted with animal in vivo, in addition to being conducted in vitro. In particular for immunity combination product with cytotoxicity or the antibody with Antibody Dependent Cell-mediated Cytotoxicity (ADCC), additional animal toxicity tests on more than one kind of animal at over-dosage or multi doses should be considered.
- 3) For products under Registration Category 8, the research information used for the determining of the dosage and the research information about the influence that the products impose on the normal bacteria should be provided. If there is any test to be exempted, the relevant information and basis for the exemption should be provided as explanations.
 - 4) For the biological products under Registration Category 13, choosing of the items to be tested should be based on a comprehensive consideration of the characteristic of the changed dosage form of the product and the relevant pharmaceutical and clinical requirements possibly arisen from such change. If some of items are to be applied for exemption, sufficient reasons shall be submitted. The items can be reduced or exempted for the following cases,

- i. When the pharmaceutical requirements are met, and there is no change in the clinical route of administration, if the basis to ensure the safety of clinical usage can be provided, then the pharmacology and toxicology information may be exempted.
 - ii. For the transforming between injections, powder for injection, and intravenous infusion, if there is no change in the clinical usage and dosage, the research information on topical tolerance may only need to be provided.
 - iii. For special dosage form such as immediate, sustained, controlled released preparations and liposome, the influence of the drug on the safety of the patient using the drugs should be evaluated based on characteristic of the biological products, safety range, characteristic of in vivo metabolite, clinical indication, people using the drugs. Usually, mainly for precaution of safety, before the clinical use, the animal pharmacokinetic comparison test at single dose should be provided to reflect the characteristic of the particular release of the preparation. This study may be exempted if there are sufficient reasons to evidence there are no concerns over the safety of the products. The relevant notes and information can be submitted to SFDA for examination together with the application for clinical.
- 5) For the preparations under Registration Category 14, if there are sufficient reasons and / or literature to evidence the in vivo metabolite and safety of the products are similar before and after the change of the route of administration, and then reduction or exemption of some of the items required for this biological product may be applied.

V Notes to the Clinical Study

- 1) A clinical trials should be conducted for the application of new drug.
- 2) Cases of patient for a clinical trials should meet the statistical requirement and minimal cases requirement.
- 3) The minimal cases requirement for a clinical trials is, Phase I: 20-30, Phase II: 100, Phase III: 300.
- 4) clinical trials for the products under Registration Categories 1-12 should be conducted in accordance with requirement for new drugs.
- 5) Only Phase III clinical trials is usually required for the products under

Registration Categories 13-15.

- 6) For the renovated sustained released preparation, comparisons study of human pharmacokinetic study and clinical trials shall be conducted.

VI Application Information and requirement for Import Therapeutic Biological Products

A Requirement for Application Information Items

Application information shall be submitted in accordance with the *Registration Application Information Items*. For the application of the preparations not yet marketed at domestic or overseas, information shall be submitted in accordance with Registration Category 1. For all other products, information shall be submitted in accordance with Registration Category 7.

B Requirement and Notes to the Information Item 2, Certified Documents

1) Information Item 2, Certified Documents includes,

- i) Certified Documents, notarized documents for the approval of the marketing of the products issued from the competent authorities at the local country or region where the manufactured is located, and the *GMP Certificate* of the manufacturer, and the Chinese translation.

For application for the product not yet marketed at domestic or overseas, the above Certified Documents can be submitted together with the clinical study report upon the completion of the clinical study in China.

- ii) When the registration of a foreign drug manufacturer is conducted by manufacturer's office in China, copies of *Registration Certificate Of Resident Office Of Foreign Enterprise* should be provided.

When a foreign drug manufacturer authorizes at domestic agent to conduct the registration, copies of the authorization document, notarized documents and the Chinese translation, as well as the Business License of the domestic agent shall be provided.

- iii) Documents and explanations to evidence the patent status and ownership of

the product, the formula of the product, the production technology and process of the product, as well as letters of guarantee stating no infringement upon the patent rights of others.

2) Notes

- i. The *GMP Certificate* and approval for the marketing of the product issued by the competent authorities at the local countries or region where the manufacturer is located, should be acknowledged by the Chinese embassy in the local countries and the public notaries in the countries.
- ii. When the preparations are manufactured in one location and packed in another location, then the Certified Documents of *GMP Certificates* of the preparations manufacturer and packing manufacturer issued by the countries where the manufacturers are located should be provided.
- iii. In the event that the products have not yet been approved to be marketed by the country or the region where the products are manufactured, then the Certified Documents from the other country where the products is approved to be marketed should be provided, and should be recognized by SFDA. But the *GMP certificates* must be issued by the competent authorities from the country where the manufacturer is located.

C Requirement for other Information Items

- 1) All the clinical study information used during the application for marketing in the local countries or region where the manufacturer is located should be submitted as Information Item 29.
- 2) All the application information should be translated into Chinese with the original language attached. The Chinese translation shall be consistent with the original language.
- 3) The Chinese translation of biological products standards must comply with the format required by the National Drug Standards of China.

D Requirements for clinical study conducted in China

- 1) A clinical study should be applied for in accordance with Registration Category 1 for the application of the biological products not yet marketed at domestic or

overseas.

- 2) A clinical study should be applied for in accordance with Registration Category 7 for the application of the biological products already marketed overseas but not yet marketed domestic.
- 3) A clinical study should be applied for in accordance with Registration Category 15 for the application of the biological products admitted with National Standards.

Part II Preventive Biological Products

I Registration Categories

- 1) Vaccine not yet marketed at domestic or overseas.
- 2) DNA vaccine.
- 3) A already marketed vaccine 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 already marketed overseas but not yet marketed domestic.
- 7) Combined vaccine prepared with vaccine already marketed domestic.
- 8) Re-combination vaccine with protective antigen spectrum different with the marketed one.
- 9) Vaccine manufactured with the change of the other approved expression or the other approved cellular stroma. Vaccine using new process, which is proved to improve the safety and effectiveness of the vaccine based on the data of laboratory.
- 10) Vaccine with change of de-activator (method of deactivation) or de-toxicitor (method of de-toxicity).
- 11) Vaccine with change in the route of administration.
- 12) A domestic marketed vaccine with change in dosage form but no change in route of administration.
- 13) Vaccine with dosage of immunity or immunity procedure.
- 14) Vaccine with an enlarged group of people (enlarged age range).
- 15) Vaccine admitted with National Standards.

II Application Information Items

- 1) Summary information
 - i. Name of the new products.
 - ii. Certified Documents.
 - iii. Objective and basis for the application.
 - iv. Sample draft of the insert sheet, notes to the draft and literature.
 - v. Sample design of the packing, label.
- 2) Research information summary and the evaluation information.
- 3) Research information of the production bacterial and toxicity strains.
 - i. Source and characteristics: including 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 including history of separation, determination and de-toxicity, characteristic, research information on the adaptability to cellular stroma, infective titer, antigenicity, immuno-genecity, toxic (or toxicity).
 - ii. 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, antigenicity, immunocity. For strain of primary generation, gene sequence should be determined.
 - iii. Stability during transfer of culture: determining of the limitation of last generation number to be used. For items to be tested, refer to the test items of batches of strains.
 - iv. Test report of batches of bacterial and toxicity strains used for production from NICPBP.
- 4) Research information of the cellular stroma for production.
 - i. 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, history (including the history of establishment of cells system,

- determining, and history of transfer of culture), biological characteristic, exogenesis factors test, analysis of karyotype, tumorigenicity test and other study.
- ii. 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, karyotype analysis and exogenesis factors inspection.
 - iii. Stability of transfer of culture: determining of 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.
 - iv. NICPBP test report of the production cells bank for cellular stroma used for manufacture.
 - v. Source and quality standards of culture fluid, additive and others, in the event that material sourced from cows is used, relevant information should be provided in accordance with requirements of SFDA.
- 5) Research information of production process and technology.
- i. Research of the production process of original fluid of the vaccine: the main technical parameters to optimize 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 potential toxic material to human, 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 and 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.
 - ii. Formula and production process of the preparations, and the basis to determine shall be provided. Source and quality standards of the supplementary shall be provided.
- 6) Research information of the quality of the product: after the determination of production process, information should be determined using statistical method, based on test results of multi batches of pilot product.
- i. Quality standards and test results of the products, including quality standards and test results of the each single component of the combined vaccine.

- ii. Research and verification information of the test method.
 - iii. Analysis information of product antigenicity, product immunocytivity and protectiveness of the animal test.
 - iv. 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, and basis for the standards should be provided.
 - v. Research information of animal hypersensitivity test.
 - vi. Comparison information with the similar product.
 - vii. Measuring of antigen components, contents, molecular weight, purity; specificity determination; and measure and test of the content (or residual) of the non-effective component.
 - viii. Information of animal safety evaluation of the product.
 - ix. For the vaccine manufactured by 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 sample product to be used for application of 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 study at domestic 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 clinical study.
 - 16) Stability research information to determine the storage and validity period of the vaccine.
 - 17) Amendments and basis to amend of the approved manufacturing and test standards.
 - 18) Record of production and testing of the 3 consecutive batches of the trial products.

B Notes to the Application Information Items

- 1) Items 1-11 shall be submitted for application of clinical study. Items 1, 2 and 12-18 shall be submitted upon completion of clinical study. Items 1, 2 and 12-17 shall be submitted for application of new drug certificate.
- 2) Summary information
 - i. Name of the new drug, including International Nonproprietary Name, English name, China adopted name and its Chinese phonetics, basis for the name. The nomenclature of the drug should be explained for any new name.
 - ii. Certified Documents includes,
 - a. Certified Documents of lawful registration of the Applicant (business licenses), copies of *Drug Manufacturing License* and change registration, *GMP Certificate*. For the application of production, copies of *GMP Certificate* for the workshop where the sample product of the drug was manufactured should be provided.
 - b. Notes stating patent status and ownership or the biological product in the application, or the formula, process to be used, and letters of guarantee stating that no infringement upon the patent rights of others.
 - c. Copy of *Approval of Clinical Study of New Drugs* and drug standards of investigative drugs should be provided for the production of new biological product.
 - d. Copies of the *Drug Packing Material and Container Certificate* or *Import Drug Packing Material and Container Certificate* for the immediate packing material and container.
 - iii. Objective and basis for the application includes the relevant literature of the current research and marketing status of the products, or summary of the production, and inoculation use at domestic and overseas, and the analysis information of renovation and feasibility of the vaccine.
 - iv. Sample of insert sheet, notes to the draft and literature includes sample draft of insert sheet drafted in accordance with the relevant regulations, notes on how all items of the draft of the insert sheet were drafted and the latest relevant literature or the latest version of the insert sheet in the original language from the original manufacturer and the translation.
- 3) The relevant technical guiding principles shall apply for the clinical study plan and clinical study protocol under Information Items 11, 12.

- 4) Information under Information Item 4 normally may be exempted for bacteria vaccine.
- 5) Information Item 6)vi) includes,
 - Comparisons with the original vaccine.
 - Comparison with the marketed vaccine.
 - Comparison between the combined vaccine and single vaccine,
- 6) Information Items 6)vii) shall be submitted for component vaccine, null cell vaccine, cracked vaccine.
- 7) Notes to Information Items 6)viii).
 - i. Toxicity reversion test study information should be provided for toxoid vaccine or vaccine used toxoid as carrier.
 - ii. Toxicity test study information should be provided based on the group of people to use the vaccine, characteristic of the vaccine, immunity dosage, and immunity procedure.
- 8) The responding category of biological products shall apply for the in vivo diagnosis biological products that regulated by the vaccine regulation.

III Table of Application Information Items

Information	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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

1. +denote the information must be submitted,
2. - denote the information may be exempted,
3. ± denote the information may or may not be required based on the particular case.

V Notes to the Clinical Study

- 1) Cases of patients (subject) for the clinical trails should meet the statistical requirement and minimal cases requirement. Minimal cases include both trial group and control group.
- 2) The minimal cases requirement for a clinical trails is, Phase I: 20-30, Phase II: 300, Phase III: 500.
- 3) For vaccine under Registration Categories 1-9 and 14, the clinical trials should be conducted in accordance with the requirement for new drugs.
- 4) For vaccine under Registration Category 10, if the research information is provided to evidence no change in the safety and effectiveness of the vaccine after the deactivation or de-toxicity of the vaccine, then normally clinical trails may be exempted.
- 5) For vaccine under Registration Category 11, a clinical trials normally should be conducted in accordance with requirement for new drugs. But the Phase I

clinical trails may be exempted for the vaccine with the route of administration changed from injections into non-injections.

- 6) Only the phase III clinical trials is needed for the vaccine under Registration Categories 12 and 15.
- 7) For the vaccine under Registration Category 13, the Phase I clinical trials may be exempted for the vaccine where the immunity procedure is changed.
- 8) For the preventive products used in infants, in principle, the sequence of Phase I clinical trails should be adults first, then children and then infants.
- 9) Each phase of clinical trail should be conducted after the completion of proviso phase in accordance with the prescribed immunity procedures.

VI Application Information and requirement for Import Preventive Biological Products.

A Requirement for Application Information Items

Application information shall be submitted in accordance with the *Registration Application Information Items*. For the application of the vaccines not yet marketed at domestic or overseas, information shall be submitted in accordance with Registration Category 1. For all other vaccines, information shall be submitted in accordance with Registration Category 6.

B Requirement and Notes to the Information Item 1) ii), Certified Documents

- 1) Information Item 1) ii), Certified Documents includes the following,
 - i) Certified Document, Notarized Document for the approval of the marketing for the vaccine issued from the competent authorities at the local country or region where the manufacturer is located, and the *GMP Certificate* of the manufacturer, and the Chinese translation.

For application for the vaccine not yet marketed at domestic or overseas, the above Certified Documents can be submitted together with the clinical study report upon the completion of the clinical study in China.

- ii) When the registration of a foreign drug manufacturer is conducted by manufacturer's office in China, copies of *Registration Certificate Of Resident*

Office Of Foreign Enterprise should be provided.

When a foreign drug manufacturer authorizes domestic agent to conduct the registration, copies of the authorization document, notarized document and the Chinese translation, as well as the *Business License* of the domestic agent shall be provided.

- iii) Documents and explanations to evidence the patent status and ownership of the biological product, the formula of the biological product, the production technology and process of the biological product, as well as letters of guarantee stating that the new drug will not infringe upon the patent rights of others.

2) Notes

- i. The *GMP Certificate* and approvals for the marketing of the product issued by the competent authorities at the local countries or region where the manufacturer is located, should be acknowledged by the Chinese embassy in the local countries and the public notaries in the countries.
- ii. When the preparations are manufactured in one location and packed in another location, then the Certified Documents of *GMP Certificates* of the preparation manufacturer and packing manufacturer issued by the countries where the preparation manufacturer and packing manufacturer are located should be provided.
- iii. In the event that the products have not yet been approved to be marketed by the country or the region where the products are manufactured, then the Certified Documents from the other country where the products are approved to be marketed should be provided, and should be recognized by SFDA. But the *GMP Certificates* must be issued by the competent authorities from the country or region where the manufacturer is located.

C Requirement for other Information Items

- 1) All the clinical study information used during the application for marketing in the local countries or region where the manufacturer is located should be submitted as Information Item 13.
- 2) All the application information should be translated into Chinese with the

original language attached. The Chinese translation shall be consistent with the original language.

- 3) The Chinese translation of vaccine standards must comply with the format required by the National Drug Standards of China.

D Requirements for clinical study conducted in China

- 1) A clinical study should be applied for in accordance with Registration Category 1 for the application of the vaccine not yet marketed at domestic or overseas.
- 2) A clinical study should be applied for in accordance with Registration Category 6 for the application of the vaccine already marketed overseas but not yet marketed at domestic.
- 3) A clinical study should be applied for in accordance with Registration Category 15 for the application of the vaccine admitted with National Standards.