

DRUG REGISTRATION REGULATION

Registration Categories and Application Information Requirements of Chemical Drugs

I Registration Categories

- 1) New chemical entity never marketed in any country.
 - i. Drug substance and its preparations made by synthesis or semi-synthesis.
 - ii. Chemical monomer (including drug substance and preparation) extracted from natural sources or by fermentation.
 - iii. Optical isomer (including drug substance and preparation) obtained by chiral separation or synthesis.
 - iv. Drug with fewer components derived from marketed multi-component drug.
 - v. New combination products.
 - vi. A preparation already marketed in China but with a newly added indication not yet approved in any country.
- 2) Drug preparation with changed administration route and not marketed in any country
- 3) Drug marketed ex-China, including:
 - i. Drug substance and its preparations, and / or with changed dose form, but no change of administration route.
 - ii. Combination preparations, and / or with changed dose form, but no change of administration route.
 - iii. Preparations with changed administration route and marketed ex-China.
 - iv. A preparation already marketed in China but with a newly added indication approved ex-China.
- 4) Drug substance and its preparation with changed acid or alkaline radicals (or metallic elements), but without any pharmacological change, and the original drug entity already approved in China.
- 5) Drug preparation with changed dose form, but no change of administration route, and the original preparation already approved in China,
- 6) Drug substance or preparation following national standard.

II Application Dossier Items

A Summary

- 1) Name of the drugs.
- 2) Certified Documents.
- 3) Objectives and basis for R & D.
- 4) Summary of main study work.
- 5) Draft of packaging insert, note to the draft, and latest literature.
- 6) Design of packaging and labeling.

B Pharmaceutical data

- 7) Summary of Pharmaceutical Study,
- 8) Research information and relevant literature of the production process of the drug substance, research information and relevant literature of formula and process of the preparations.
- 9) Study information and relevant literature for the chemical structure and components determination.
- 10) Study information and literature for quality specification.
- 11) Draft of quality specification and notes, and providing reference standard.
- 12) Test report of drug sample.
- 13) The source, test report and quality specification of drug substance and excipient.
- 14) Stability study and relevant literature.
- 15) Selection basis and quality specification of immediate packing material and container.

C Pharmacology and toxicology study information.

- 16) Summary of pharmacology and toxicology study.
- 17) Primary pharmacodynamics study and literature.
- 18) General Pharmacology study and literature.
- 19) Acute/single dose toxicity study and literature.
- 20) Repeated dose toxicity study and literature.
- 21) Special safety study and literature of hypersensitive (topical, systemic and photo-toxicity), hemolytic and topical irritative (blood vessel, skin, mucous

- membrane, and muscle) reaction related to topical and systemic use of the drugs.
- 22) Study and relevant literature on Pharmacodynamics, toxicity and pharmacokinetics change caused by the interactions amongst multiple components in the combination products.
 - 23) Study and literature of mutagenicity test.
 - 24) Study and literature of reproductive toxicity.
 - 25) Study and literature of carcinogenicity test.
 - 26) Study and literature of drug dependence.
 - 27) Study and literature of pre-clinical pharmacokinetics.

D Clinical Study Information

- 28) Summary of global clinical study information.
- 29) Clinical study protocol.
- 30) Investigator's Brochure.
- 31) Draft of Informed Consent Form, approval of the Ethics Committee.
- 32) Clinical study report.

III Notes to Application Information Items

- 1) Information Item 1, Name of the drugs, includes International Nonproprietary Name (INN), Chemical Name, English Name, and Chinese Phonetics. Chemical structure, Molecular Weight, Molecular Formula shall be noted. The Nomenclature of the drug should be explained for any new name.
- 2) Information Item 2, Certified Documents, includes,
 - i. Certified Documents of lawful registration of the Applicant, copies of *Drug Manufacturing License, GMP Certificate*. For the application of production of new drugs, copies of *GMP Certificate* for the workshop where the sample product of the drugs was manufactured should be provided.
 - ii. Certified Documents stating patent status and ownership of this entity and formula, production process of the drug, and letter of guarantee stating that no infringement upon the patent rights of others.
 - iii. Copies of official approvals of the research proposal of narcotics, psychotropic, medical-use toxic drugs and radioactive drugs.
 - iv. For the application of production of new drugs, copy of *Approval of Clinical*

Study of New Drugs and the quality standard of investigational drugs should be provided for the market authorization approval.

- v. For the application of production of preparation, certified documents to evidence the legal channels of drug substance should be provided, including copies of certified approval document of drug substance, drug standards, test report, business licenses of manufacturers of drug substance, *Drug Manufacturing License*, *GMP Certificate*, sales invoice, and supply contract.
 - vi. Copies of the *Drug Packing Material and Container Certificate* or *Import Drug Packing Material and Container Certificate* for the immediate packing material and container.
- 3) Information Item 3, objectives and basis of the application, includes R&D, marketing status, and the related literature of the drugs, as well as the summary of the use and production of the drugs, domestically and overseas,
 - 4) Information Item 4, summary and evaluation of main research results, includes the summary of main research results by the Applicant, and a comprehensive analysis of safety, efficacy, and quality controllability of the drugs of the application.
 - 5) Information Item 5, draft of insert sheet, notes to the draft and latest literature, includes the sample of draft of packaging insert sheet drafted in accordance with the relevant regulations, notes on how each items of the insert sheet were drafted, latest relevant literature.
 - 6) Information Item 7, Summary of Pharmaceutical Study, refers to the summary of experiment and global literature of Pharmaceutical Study of the drug in the application (synthesis process, selection of dosage form, screening of formula, determination of structure, quality study and determination of quality standards, and stability study).
 - 7) Information Item 8, research information of the production process of the drug substance, includes technology process and chemical reaction equation, initial raw material and organic menstruum, reaction conditions (temperature, pressure, duration, catalyst) and operation procedure, refining method and main physical-chemical constants. The raw material input, and output yield, as well as possible impurities or other by-products produced or mixed during the production process should be explained.
 - 8) Information Item 10, experiments information and literature for quality research, includes physical-chemical properties, purity inspection, dissolution, assay, and methodology validation, as well as the data and results collected at various stages.
 - 9) Information Item 11, draft of drug quality specification and notes, and reference

standard shall be provided: Quality specification shall comply with the format of the current version of *Chinese Pharmacopoeia*, and the terminology and units of measure of *Chinese Pharmacopoeia* should be used. Reagents, reagent solution, buffer solution, titrant and others used and their concentration should follow the current version of *Chinese Pharmacopoeia*. In the event of a different one was used, detailed explanations should be provided. Reference standard shall be provided with separate information attached to explain the source, physical-chemical constants, purity, content, and measurement method and data of the drugs.

Notes to the draft of drug standards shall include the selection of items to be controlled, selection of method, inspection and purity and limitation range, as well as the basis to decide each item.

- 10) Information Item 12, the test report of the sample products, means the self-test report of the sample products of the drugs in the application. Self-test report for at least one batch of sample product should be provided before the clinical study. Self-test reports of the consecutive 3 batches of sample products should be provided for the market authorization approval after completion of the clinical study.
- 11) Information item 14, experiments information and literature of the stability study of the drugs, includes stability test conducted together with the use of the immediate packing material and container.
- 12) Information item 16, Summary of pharmacology and toxicology study, refers to the summary of experiment and global literature of pharmacology and toxicology study of the drug in the application (including pharmacodynamics, mechanism of action, general pharmacology and toxicology, and pharmacokinetics).
- 13) Information item 27, summary of pre-clinical pharmacokinetics, refer to the summary of experiment and literature of pre-clinical pharmacokinetics (animal) of the drug in application (absorption, metabolite, distribution, excretion)
- 14) Information item 28, Summary of global clinical study information, refers to summary of global literature, abstract and latest updating regarding the clinical trial of the drug in the application.
- 15) Information item 29, Clinical study protocol: Clinical study protocol should cover details to deal with the critical items including proposed indication, usage and dosage, which should be supported with submission of study information. Clinical study protocol should be scientific, complete and there should be a comprehensive

summary of pre-clinical and clinical information related to the key analysis of the potential risks and benefit of proposed trials.

- 16) Information item 29, Investigator's Brochure, refers to summary of existing pre-clinical and clinical information of the drug in the application, for the purpose to provide Investigator and other participators with information to aid them in understanding the characteristic of the drug and Clinical study protocol. Investigator's Brochure should be concise and objective.

IV Table of Application Information Item and Notes
 A Table of Application Information Item

Information category	information item	Registration category and information item requirement					
		1	2	3	4	5	6
Summary information	1	+	+	+	+	+	+
	2	+	+	+	+	+	+
	3	+	+	+	+	+	+
	4	+	+	+	+	+	+
	5	+	+	+	+	+	+
	6	+	+	+	+	+	+
Pharmaceutical Information	7	+	+	+	+	+	+
	8	+	*5	+	+	*5	*5
	9	+	+	+	+	+	+
	10	+	+	+	+	+	+
	11	+	+	+	+	+	+
	12	+	+	+	+	+	+
	13	+	+	+	+	+	+
	14	+	+	+	+	+	+
	15	+	+	+	+	+	+
Pharmacology and toxicology study information	16	+	+	+	+	+	+
	17	+	*16	±	*18	—	—
	18	+	*16	±	*18	—	—
	19	+	*16	±	*18	—	—
	20	+	*16	±	*18	—	—
	21	*19	*19	*19	*19	*19	*19
	22	*13	—	—	—	—	—
	23	+	±	±	±	—	—
	24	+	±	±	±	—	—
	25	*8	—	*8	*8	—	—
	26	*9	—	—	—	—	—
27	+	*20	*20	+	*20	—	
Clinical Study information	28	+	+	+	+	+	+
	29	+	+	+	+	+	△
	30	+	+	+	+	+	△
	31	+	+	+	+	+	△
	32	+	+	+	+	+	△

Notes:

1. + Denote the information must be submitted,
2. ± Denote literature can be used instead of test information,
3. – Denote the information may be exempted,
4. * Denote the information shall be submitted according to the requirement, *8 refer to note 8.
5. △ denote that the provisions 4 of “V , Requirement For Clinical Study” shall apply.
6. literature refers to literature and / or summary of literature of all Pharmacology and toxicology study information of the drug in the application (including pharmacodynamic, mechanism of action, general pharmacology and toxicology and pharmacokinetics)

B Notes

- 1) Drugs under Registration Categories 1-5 refer to as new drugs. Drugs under Registration Category 6 refer to as the drugs already following National Standards. New indications referred in Registration Categories 1.6 and 3.4 mean the cases where preparation already marked in China add new indications.
- 2) Information Items 1-30 (except Information Item 6) shall be submitted for the application for new drugs as required under the *Table of Application Information Items*. Re-compiled summary Information Items 1-6, Information Item 12 and 14, clinical Information Items 28-32 and other changes and supplemental information shall be submitted and numbered with the numbers of Information Items upon the completion of the clinical study.

For the drugs under Registration Category 1, upon the completion of the clinical study, all the required information of Information Items 1-30 should be re-edited according to the result of trails conducted during clinical study, and then be re-submitted.

When the registration of drug substance and registration of preparation of the chemical drug under Registration Category 3 and 4 are applied at the same time, the registration of drug substance should comply with the requirement for production.

- 3) Information Items 1-16 and 28-30 shall be submitted for the application for a drug already with National Standard as required under the *Table of Application Information*

Items. If the clinical study was required, upon completion of the clinical study, Information Items 28-32 and other changes and supplemental information shall be submitted and numbered with the numbers of Information Items.

- 4) During the registration of the drug already with National Standards, there should be a comprehensive quality study of the process and formula of the drug, and quality comparison with the already marketed drugs according to the national standards. When it is not possible to conduct the quality comparison with the already marketed drugs according to the national standards, a quality study should be conducted according to the requirement for registration of new drug, and if necessary, quality provisions in the national standard can be appended and /or revised.
- 5) During the application only for preparations, the lawful Certified Documents to evidence the lawful sourcing of the drug substances shall be provided in 2 duplicates, which should be respectively categorized into information item 2 (certified document) and information item 13 (The source, test report and quality specification of drug substance and excipient). For the applicant using domestic drug substance, the documents that should be provided include copies of certified approval document of drug substance, drug standards, test report, business licenses of manufacturers of drug substance, *Drug Manufacturing Certificate*, and *GMP Certificate*, supply contract signed with manufacturers of drug substance, purchasing receipts. When the import drug substances were used, copies of supply contract signed with manufacturers of drug substance or its legal domestic agent, *Import Drug Certificate*, or *Pharmaceutical Product Certificate*, test report from Drug Control Institute of the local Customs, and drug standards shall be provided. During drug registration, use in investigative preparation with the drug substances without *Import Drug Certificate*, or *Pharmaceutical Product Certificate* must be approved by SFDA.
- 6) For the registration of the drugs transformed among injections, powder for injection and intravenous infusion, the application shall be applied by the qualified enterprise with the production scope of the corresponding dosage form.
- 7) The reproductive toxicity research information corresponding to the drug used for the people at child-bearing age should be submitted based on the natures of the indications and characteristic of the new drug
- 8) For any of the drugs with expected treatment period longer than 6 months inclusive, or used for treatment of chronic and recurrent disease, or intermittent use for a regular period of time, experiment information or literature on Carcinogenicity should be provided, and information of carcinogenicity test or literature should be submitted for the following new drugs, based on the indication and characteristic of

action:

- i. New drugs with chemical structure relating to the known carcinogen or the metabolite of the new drugs are similar to the known carcinogen.
 - ii. During long-term toxicity experiment, cytotoxic effects were shown or extraordinary activation on the growth of cells in certain visceral organs and tissues were caused.
 - iii. Drug with a positive test result during mutagenicity test.
- 9) For new drugs acting on central nervous system, such as analgesics, depressants, stimulants, and drugs with chemical structure related to those compounds liable to cause drug dependence, experiment information of drug dependence should be submitted.
 - 10) For the new drug under Registration Category 1, toxicokinetics study should usually be conducted during the repeated doses toxicity study.
 - 11) Under the Registration Category 1, the optical isomer obtained from a known drug through chiral separation or synthetic method and its preparation, the research information and relevant literature compared between racemate and mono-isomer in areas on pharmacodynamics, pharmacokinetics and toxicology (normally acute toxicity) should be provided to indicate the justification of the R&D. When the safety range of racemate is narrow, and the available information indicates that the unexpected toxicology (irrelevant to pharmacology) is considerably high, the toxicology test of mono isomer with repeated doses (normally lasting for 3 months) or other toxicology tests (such as reproductive toxicology) shall be provided based on the comprehensive information such as clinical course of treatment, dosage, and indications of the drugs, as well as the people using the drugs.
 - 12) For drugs under Registration Category 1 with fewer components derived from already marketed multi-component drugs, if the component did not include the substance explained in note 8 herein, then Information Items 23-25 may be exempted.
 - 13) For the new combination products under Registration Category 1, Information Item 22 should be submitted.
 - 14) For the new combination products under Registration Category 1, information of toxicity test of repeated dosage compared with single dosage should be provided, and if the - toxicity test of repeated dosage indicated no increase in toxicity, and no change in the target tissue, Information Item 27 should be exempted.
 - 15) For the new combination products under Registration Category 1, if there is no significant change in animal pharmacokinetic study results, then Item 23-25 should

be exempted.

- 16) For the new drugs under Registration Category 2, the route of administration during the pharmacology and toxicology study should be the same with that to be used in clinical study. Generally, the pharmacokinetic test or the related toxicology study information (such as topical and repeated dose toxicity) compared with the original route of administration should be provided.
- 17) For the drugs under Registration Category 3, the preparations with change in route of administration and already marketed overseas, emphasis should be focused more on the drug absorption or topical toxicity influenced by the excipient, and if necessary, the pharmacokinetic test or other toxicology study should be provided.
- 18) For the new drugs under Registration Category 4, pharmacokinetic, main pharmacodynamic, normal pharmacology and acute toxicity test information compared with the already marketed drugs should be provided to reflect the difference before and after the changes, and if necessary, the research information on repeated doses toxicity and other relevant pharmacology and toxicology study should be provided. If the preparation is made by changing the acidic or alkaline radicals (or metallic elements) of the salt of a marketed drug, it has been already marketed overseas, then the application information requirement under Registration Category 3 shall be provided.
- 19) For the drugs for topical use, in addition to the information required under the relevant Registration Category and Information Items, the information under Information Item 21 should also be submitted; topical absorption test should be conducted, if necessary.
- 20) When there is an obvious safety concerns in the immediate, sustained and controlled released preparations (narrow safety range, significant increase in dosage), animal pharmacokinetic study information compared with the marketed immediate, sustained and controlled released preparations regular preparations should also be provided at single dose.

V Requirement for Clinical Study

- 1) For the new drugs under Registration Category 1 and 2, clinical trials should be conducted.
 - i. Cases of patients for clinical trials should meet the statistical requirement and the minimal cases required.
 - ii. The minimal cases required (trial group) of clinical trials are as following, 20-30 for

- Phase I, 100 for Phase II, 300 for Phase III, 2000 for Phase IV,
- iii. Phase I clinical trial of the contraceptives should be conducted following this Regulation. In Phase II clinical trial, a randomized controlled clinical study should be conducted on at least 100 pairs of subjects for at least 6 menstruation cycles. In Phase III trial, an open trial on at least 1000 cases for 12 menstruation cycles should be accomplished. In Phase IV trial, variable factors of such kind of drugs should be carefully considered to finish the trial with adequate numbers of cases.
 - 2) For the new drugs under the Registration Categories 3 and 4, human pharmacokinetic study and randomized controlled clinical trials on at least 100 pairs of subjects should be conducted. In the event of more than one indication, cases for each main indication shall not be less than 60 pairs. Human pharmacokinetics study and an open trial on at least 500 cases for 12 menstruation cycles should be accomplished for contraceptives.

Human pharmacokinetics study may be exempted for the following 2 cases:
preparation of topical use with only topical treatment effect.
oral preparation that not be absorbed.

- 3) The clinical study for the new drug under Registration Category 5 should be conducted in accordance with the following principles,
 - i. Bioequivalence trials should be conducted for oral solid preparations on normally 18-24 cases.
 - ii. When a bioequivalence trial is difficult to be conducted for oral solid preparations or other non- oral solid preparations, clinical trials should be conducted, and cases for the clinical trials should be at least 100 pairs.
 - iii. For the preparations of sustained and controlled released preparations, controlled human pharmacokinetic study and clinical trials related to therapeutics should be conducted on single dose and repeated doses of the drugs, and the cases for clinical trials should be at least 100 pairs.
 - iv. For registration of drug transformed among injections, powder for injection and intravenous infusion, if the route of administration, dosage, and usage are identical with the original dosage form, the clinical study can be exempted.
- 4) For the oral solid preparations under the Registration Category 6, bioequivalence tests should be conducted on normally 18-24 cases.

If the quality of drug needs to be controlled by process and standards, clinical tests should be conducted on normally 100 cases.

- 5) During the new drug registration of chemical drug, when at the same time the registration of injection, powder injection and intravenous infusion that made of this chemical drug is also applied, if the preparations are from the same applicant, clinical trial is only needed for one of the preparation. For other preparation, as long as requirement of exemption of clinical trail are met, clinical trail may be exempted. If the preparations are from different applicants, clinical trail should be conduction respectively.
- 6) Application for reduction or exemption of clinical trial should be made during the application of drug registration with detail of reasons and information for reduction or exemption of clinical trials. If a clinical trial is already approved, with exception of the case where reduction or exemption of clinical trial is allowed by this *Regulation*, reduction or exemption of clinical trial generally should not be allowed. If there is indeed difficulty to complete the clinical trial, application should be made with detail of the basis and plan for reduction or exemption of clinical trial, where the rational should be justified in term of clinical statistic, status of group of patients in the clinical trials.
- 7) The comparative drug used for the controlled clinical trails shall be already marketed in China. If the comparative drug must be imported, there need to be approval from SFDA. Priority in choosing the comparative drug of positive clinical test should according to the following:
 - i. Drug from the original manufacturer
 - ii. The same drug of definite clinical test data
 - iii. Drug of the same active substance and route of administration but different dosage form
 - iv. Other drug of similar mechanism of action effect and the same indication.

VI Requirement on Import Chemical Drug.

A Requirement of Application Information Items

- 1) Application Information should be submitted in accordance with the requirement under *Table of the Application Information Items* of Chemical Drugs. For the application of the new chemical entity not yet marketed in any country, Application Information should be submitted in accordance with the Registration Category 1. For other drugs, Application Information should be submitted in accordance with the Registration

Category 3. Drug under Registration Category 1 refers to those that are at least in the stage of Phase II Clinical Trials ex-China.

- 2) Information Item 5, include draft of packaging insert sheet, notes to the draft and the updated literature, the original PI from the manufacturing country, the actual commercial sample of PI used in the manufacturing country and the Chinese translation. The original commercial packaging and labeling should also be provided for Registration Category 6.
- 3) All the clinical study information used for the market authorization approval in the original manufacturing countries shall be submitted for Information Item 28.
- 4) All the application information shall be in Chinese with the original text attached, information in other language (ex-English) may be attached as reference. The Chinese translation shall be consistent with the original language.
- 5) The Chinese translation of quality specification must comply with the format of the National Drug Standards of China.

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

- 1) Information Item 2, Certified Documents, includes,
 - i) Certified Documents, notarized document for the free sale certificate (FSC) issued from the competent authorities of the local country or region where the manufacturer is located, and the *GMP Certificate* of the manufacturer, and the Chinese translation.

Application for the drugs under Registration Category 1, the above Certified Documents can be submitted together with the clinical study report upon the completion of the clinical study in China. However, during the application of Clinical Trails, certified documents of *GMP Certificate* of the manufacturer issued by local competent drug administration where the drug is manufactured must be provided.

- 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 drugs of the application, the formula of the drugs, the production technology and process of the drugs, as well as letters of guarantee stating that the new drug will not infringe upon the patent rights of others.

2) Notes,

- i) Certified Documents, notarized document for the FSC and *GMP Certificate* of the manufacturer should comply with the recommended format by World Health Organization (WHO). The document in other format must be legalized by the Chinese embassy in the original country.
- ii) When the manufacturing site and packaging site separated, the Certified *GMP Certificates* of manufacturing and packaging site issued by the corresponding countries should be provided.
- iii) In the event that the products not yet approved in the manufacturing country or region, the Certified Documents from the country where the products being marketed and *GMP Certificates* from this country could be provided. The Certified Documents from the country where the products being marketed and *GMP Certificates* from this country should be recognized by SFDA.
- iv) For the drug substance, the Certified Documents for the approval of the marketing for the drug substance or its preparation issued by the competent authorities of the original manufacturing country, and the *GMP Certificate* of the manufacturer should be provided. Drug Master File (DMF) or Certificate of Suitability to the Monographs of the European Pharmacopoeia of the drug substance may also be accepted.
- v) To apply for an international multi-center clinical study, certified document of *GMP Certificate* of the drug manufacturer issued by local drug administration where the manufacturer is located must be provided.
- vi) For drug substance or preparation, whenever applicable, certified document of *GMP Certificate* of the drug manufacturer issued by local food and drug administration where the manufacturer is located, ISO9000 quality assurance

certificate issued by the competent organization, and / or free sale certificate (FSC) issued from the competent authorities of the local country or region where the manufacturer is located should be provided

C Requirement for the clinical study conducted in China

- 1) During application of drug never marketed in any country, clinical trials should be conducted according to CT study requirement of Registration Category 1.
- 2) During application of drug that marketed ex-China but not in China, clinical trials should be conducted according to CT study requirement of Registration Category 3.
- 3) During application of drug with same route of administration but different dosage form of that of the drug marketed in China, if information item 28 of the application meet the requirement, clinical trials should be conducted according to CT study requirement of Registration Category 5. If information item 28 of the application did not meet the requirement, clinical trials should be conducted according to CT study requirement of Registration Category 3.
- 4) During application of drug already with National Standards, if information item 28 of the application meet the requirement, clinical trials should be conducted according to CT study requirement of Registration Category 6. If information item 28 of the application did not meet the requirement, clinical trials should be conducted according to CT study requirement of Registration Category 3. No clinical trial is needed for application of drug substance already with National Standards.
- 5) For the application only for the importation of the drug substance without available National Drug Standards in China, the clinical study shall be conducted with the use of the preparations of the drug substance.

VII Application Information and Requirement for Radioactive Drugs

A Requirement of Information Items

- 1) For the application of radioactive drugs, the application information shall be prepared for nuclide, drug substance, packing case and preparations respectively, and be in accordance with the corresponding Category of chemical drugs, and the Requirement of *Application Information Items*. Information Items 22 and 26 may be exempted.
- 2) For the application of diagnosis radioactive drugs, Information Items 23, 24 and 25 may be exempted.

- 3) For the application of radioactive chemicals and packing case, Information Item 17 and 18 may be exempted. Information required under preparation should also be provided for the application of packing case.

B Notes to the Information Items

- 1) Information Item 8 shall be submitted in accordance with the following,
 - i) Radioactive chemicals: the selection of the production method of the nuclide, irradiation condition, nuclear reaction equation, chemical processing technology after target material irradiated (with the chemical reaction equation and production process attached), detailed operation procedure, possible nuclear impurity introduced, refining (purifying) method, and the specification, standards and analysis of the other chemical reagent (in particular target material), relevant literature and information at domestic and overseas should be provided.
 - ii) Packing case: the experiment basis for the determining of packing case, the preparation process, route, reaction condition, operation steps and quality standards of all components of the packing case shall be provided. If any components was made by the manufacturer, then the basis of determining of the detailed synthesis route, synthesis process flow, reaction equation, chemical equation, reaction condition, operation procedure, material input, output ratio, and possible impurity introduced and mixed, quality control of the intermediate products at each steps, refining (purifying) method of finished product, quality standard of the raw material, literature and information at domestic and overseas shall be provided.
 - iii) Preparation: basis to choose the formula of the preparation, preparation process, reaction condition, operation procedure, refining or purifying method, quality standards and analysis and test data of raw material, and literature and information at domestic and overseas shall be provided.
- 2) Information Item 9 shall be submitted in accordance with the following,
 - i) Radioactive chemicals: global literature and experiment data (illustrating spectrum and a comprehensive interpretation) used to determine the structure should be provided. If the radioactive nuclide of the radioactive drug is not yet listed in the *Chinese Pharmacopoeia*, then the decay illustrating chart of the nuclide, experiment data (or spectrum) to determine the nuclear characteristic, as well as experiment information and literature compared with the nuclear characteristic

- of the nuclide widely recognized at domestic and overseas should be provided.
- ii) Packing case: The detailed component and usage of the packing case should be provided, with explanation of the function of each and every components of the packing case. If any components was made by the manufacturer, then global literature and the detailed experiment data (illustrating spectrum and a comprehensive interpretation) used to determine the structure should be provided.
 - iii) Preparation: Experiment data to determine the chemical structure should be provided. If there is a difficulty to provide, the reason should be explained and reasonable logic can be used to conclude the possible chemical structure or quote the relevant literature that can be used as basis.
- 3) Information Item 10 shall be submitted in accordance with the following,
- i) Radioactive chemicals: research items for the physical-chemical constants, items of the purity testing, the screening of the method to measure the content, and the basis to determine the method should be provided with details of the measuring method, and measuring data.
 - ii) Packing case: the analyzing and measuring method, principle and data of the characteristic, determination, clarity, and PH value of the solutions should be provided. Determining of the content measuring method, the experiment data, testing method for bacteria, intracellular toxicity, and the research information to decide the limitation should be provided.
 - iii) Preparation: determining method and experiment data of the physical-chemical properties, characteristic, determining and principle, PH value, radioactive nuclear purity (including main nuclear impurity), radioactive chemical purity, radioactivity, chemical purity of the drug should be provided. For the injection, methods used for testing for bacteria, intracellular toxicity, data, basis to determine the limitation of intracellular toxicity should be provided.
- 4) Information Item 17 shall be submitted in accordance with the following,
- i) For the diagnosis radioactive drug, information about the testing and measuring method, testing conditions and result explanation of image of the target organ and whole body planar image should be provided. The image picture or its copies of the development at all phase of test, as well as the function measuring

result should be provided.

- ii) For the therapeutically radioactive drug, experiment information of animal experimental model within the main indications should be provided, , detailed global literature of pharmacodynamic study of the drug or other similar drug should also be provided.

5) Information Item 19 shall be submitted in accordance with the following,

Acute toxicity test should be conducted on mouse for the drug substance of radioactive drug under Registration Categories 1 and 3 packing case and preparations should be tested with abnormal toxicity test. If there is only a limited quantity produced from refining and synthesis of the drug substance and there is only a trivial clinical usage, then the abnormal toxicity test may also be adopted.

6) Information Item 20 shall be submitted in accordance with the following,

- i) For the radioactive drug under Registration Category 1, experiment information and literature of long-term toxicity test and medical internal irradiation absorption dose (MIRD) on rat and dog should be provided.
- ii) For the radioactive diagnosis and therapeutic radioactive drug under Registration Category 1, internal irradiation absorption dose after the full decay of the radioactive nuclide of the drug, estimation of absorption dose of the human target organ and non-target organ, or the literature of the drug or similar drug at domestic and overseas should be provided.

C Requirement of Clinical Study

The clinical study of the radioactive drug should be conducted in accordance with the corresponding Category of the chemical drugs. In some special case, cases of clinical trials may be adjusted to an appropriate level subject to the statistical requirement.

D Definition

Radioactive chemicals, packing case and preparation referred in this provision have the following definition:

Radioactive chemicals: means the material of Radioactive Nuclide, which will be directly used for the preparation of radioactive drug preparation.

Packing case: a collective name for unidentified ligand, reducing agent, oxidant, separator,, which will be used as auxiliary of the radioactive chemicals for the purpose of quick preparation before any application.

Preparation: refers to the radioactive drug made of Radioactive Nuclide and other substance.

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