appendix

Biological product registration classification and application data requirements

Biological products refer to microorganisms, cells, animal or human tissue and body fluids, etc.
Starting materials, prepared by biological techniques, for the prevention, treatment and diagnosis of human diseases
sick preparations. In order to standardize the registration declaration and management of biological products, biological products are divided into pre-
Preventive biological products, therapeutic biological products and in vitro diagnostic tests regulated by biological products
agent.

Preventive biological products refer to the prevention and control of the occurrence and prevalence of diseases.
Vaccine biological products for human immunization, including immunization program vaccines and non-immunization programs
Vaccination.

Therapeutic biological products refer to biological products used for the treatment of human diseases, such as
Engineered cells with different expression systems (e.g. bacteria, yeast, insects, plants and mammals
proteins, polypeptides and their derivatives prepared from biological cells); cell therapy and gene therapy
therapeutic products; allergen products; microecological products; human or animal tissue or body
Liquid extraction or biologically active products prepared by fermentation, etc. biological products
In vivo diagnostic reagents are managed as therapeutic biological products.

In vitro diagnostic reagents regulated as biological products include in vitro diagnostic reagents for blood source screening
In vitro diagnostic reagents, radionuclide-labeled in vitro diagnostic reagents, etc.

The drug registration classification is determined when the marketing application is submitted, and no other
Changes due to drugs being marketed at home and abroad.

Part I prophylactic biological products

1. Registration classification

Category **1 :** Innovative vaccines: Vaccines that have not been marketed at home and abroad: 1.1 Vaccines that do not have effective means of preventing diseases. 1.2 New antigen forms developed on the basis of marketed vaccines, such as new genetic recombinant vaccines, new nucleic acid vaccines, and new conjugate vaccines prepared on the basis of marketed polysaccharide vaccines.

1.3 Vaccines containing new adjuvants or new adjuvant systems. 1.4 Polyvalent/multivalent vaccines containing neoantigens or neoantigens. Category **2 :** Improved vaccines: Vaccines that have been marketed domestically or overseas to improve the safety, efficacy and quality controllability of new products and have obvious advantages, including: 2.1 Vaccines that have been marketed domestically or overseas Vaccines that change the antigenic spectrum or type on the basis of marketed products and have obvious clinical advantages. 2.2 Vaccines with major technical improvements, including improvements to vaccine strains/cell substrates/ production processes/formulations, etc. (such as replacing vaccines with other expression systems or cell matrices; changing strains or modifying marketed strains; modifying marketed cell matrices or target genes; improving non-purified vaccines to purified vaccines; improving whole-cell vaccines for component vaccines, etc.)

2.3 New polyvalent/multivalent vaccines composed of vaccines with similar products on the market. 2.4 Vaccines with obvious clinical advantages by changing the route of administration. 2.5 Change the immunization dose or immunization schedule, and the new immunization dose or immunization schedule Vaccines with clear clinical advantages.

2.6 Change the vaccine for the applicable population.

Category 3: Vaccines that have been marketed domestically or overseas:

3.1 The vaccines produced overseas that have been marketed overseas and have not been marketed in China should be declared for marketing. 3.2 Vaccines that have been marketed overseas but have not been marketed in China shall be declared for production and marketing in China. 3.3 Domestically marketed vaccines. 2. Requirements for application materials

For supporting documents, refer to the relevant acceptance review guidelines. For vaccine clinical trial applications and marketing registration applications, applicants should follow the "M4: General Technical Document (CTD) for Human Drug Registration Application" (hereinafter referred to as CTD) Write application materials. See Annex for regional information 3.2.R requirements. The specific content of the application materials should not only meet the requirements of the CTD format, but also meet the requirements of the continuously updated relevant regulations and technical guidelines. According to the law of drug research and development, in different stages of application, pharmaceutical research, including process and quality control, is a process of gradual progress and improvement. Different biological products also have their own pharmaceutical characteristics. If the applicant believes that it is not necessary to submit one or some of the studies required for the application, it should be marked as not applicable, and sufficient evidence should be provided.

The requirements for biological products in ICH M4 are mainly for genetically engineered recombinant products, Depending on the characteristics of vaccine research, it is also necessary to consider:

Pharmaceutical aspects: 1. Consideration of pharmaceutical data of different types of vaccines On the basis of the basic framework of ICH M4, they should be submitted for production according to the characteristics of vaccines. Bacteria (virus) species, process development, process description, quality characteristics research and other information.

2. Consideration of seed lot and cell matrix

For vaccine applications involving virus strains, it should be submitted in Section 3.2.S.2.3

Information on the production of poisonous species.

In 3.2.S.2.3, provide seed batches for production (viral) seeds and cell substrates for production

Review by a third-party inspection agency recognized by the China Institute for Seed Approval or relevant drug regulatory agencies

Verification report.

3. Adjuvants

Adjuvant-related research data are submitted to the following two sections: Submission of Adjuvants in 3.2.P

overview; submit complete pharmaceutical research information in 3.2.A.3, including raw materials, process

technology, quality attributes, detection methods, stability, etc.

4. Safety evaluation of exogenous factors

A systematic analysis of exogenous factor safety should be performed in accordance with relevant technical guidelines. overall

For traditional vaccines, refer to the relevant requirements of vaccines, and recombinant vaccines can refer to recombinant therapeutic products.

Product related requirements.

Target virus inactivation validation data are submitted in section 3.2.S.2.5 Process Validation.

Non-target virus removal/inactivation validation studies in 3.2.A.2 Exogenous Agent Safety

Submitted in the evaluation section.

5. Polyvalent/multivalent vaccines

For multivalent vaccines, according to the differences in the production process and quality control of each type of component

Consider the organization of the application materials, if they are similar, they can be listed in the same chapter 3.2.S

Section 3.2.S can be submitted separately if the differences are significant.

When the product contains multiple components (such as combination vaccines, or with diluents),

A complete stock and/or formulation section can be provided for each component separately.

Non-clinical research: 1.

Adjuvant For adjuvant, if there is

pharmacokinetic and toxicological research, submit it in the corresponding section according to the basic framework of ICH M4; the type of adjuvant used, the necessity of adding adjuvant and the adjuvant/antigen ratio is reasonable The research contents such as property and adjuvant mechanism are submitted in the main pharmacodynamics section of 4.2.1.1.

2. The rationality of the multiple/

multivalent vaccine antigen ratio and the cross-protection activity of the polyvalent vaccine antibody The content of the sexual research is submitted in 4.2.1.1 Main Pharmacodynamics

section. 3. Others In addition to routine safety studies, other safety studies

can be submitted in the section 4.2.3.7 Other toxicity studies. **For clinical trials:** "Test report of investigational drug and record of trial production of investigational drug (including placebo)" should be included in "E3: 9.4.2 Identification of

investigational product", and the specific information is in "16.1" of "16. Appendix" .6 If more than 1 batch of drug is

used, submit in "List of Patients Who Received a Specified Batch of Investigational Drug/Investigational Product". When the applicant completes the clinical trial and submits the application for drug marketing registration, it shall submit the clinical trial database in the form of a CD-ROM on the basis of the CTD. For specific requirements such as database format and related documents, please refer to the relevant guidelines for clinical trial data submission. Overseas applicants who apply

to conduct clinical trials of vaccines for minors in China should obtain at least phase I clinical trial data involving target populations abroad. Except for vaccines that are urgently needed in response to major public health emergencies or those identified as urgently needed by the competent health department of the State Council.

Part II Therapeutic biological products 1. Registration

classification Category **1 :** Innovative biological products: therapeutic biological

products that have not been marketed at home and abroad. Category **2 :** Improved biological products: therapeutic

biological products that improve the safety, efficacy, and quality controllability of new products by improving products that have been marketed in China or abroad, and have obvious advantages. 2.1 On the basis of the marketed products, the formulation and route of administration are optimized, and the biological products have obvious clinical advantages. 2.2 Add new indications

and/or change the drug population that have not been approved at home and abroad. 2.3 The biological products that have been marketed with similar products form new compound products. 2.4 On the basis of marketed products, biological products

with major technical improvements, such as recombinant technology replacing biological tissue extraction technology;

compared with marketed products, it has obvious clinical advantages after changing amino acid sites or expression

systems and host cells.

Category 3: Domestic or overseas listed biological products: 3.1

The overseas listed biological products produced overseas and domestic unlisted biological products are listed on the declaration city.

3.2 The biological products that have been listed overseas and not listed in China are declared for domestic production city.

3.3 Biosimilars. 3.4 Other

biological products. 2. Requirements

for application materials

1. For the clinical trial application and marketing registration application of therapeutic biological products, the applicant should write the application materials in accordance with "M4: General Technical Document (CTD) for Human Drug Registration Application" (hereinafter referred to as CTD). See Annex for regional information 3.2.R requirements.

2. The specific content of the application materials should not only meet the requirements of the CTD format, but also meet the requirements of the continuously updated relevant regulations and technical guidelines. According to the law of drug research and development, in different stages of application, pharmaceutical research, including process and quality control, is a process of gradual progress and improvement. Different biological products also have their own pharmaceutical characteristics. If the applicant believes that it is not necessary to submit one or some of the studies required for the application, it should be marked as not applicable, and sufficient evidence should be provided.

3. For biosimilars, the content of the quality similarity evaluation section can be submitted in "3.2.R.6 Other Documents". 4. For antibody drug conjugates or modified products, the pharmaceutical research materials of small molecule drugs can be submitted separately in accordance with the requirements of CTD format and content, or all pharmaceutical research materials can be submitted in "3.2.S.2.3 Material Control" research material.

5. For compound products or multi-component products, each component can be submitted separately.
See the entire stock solution and/or preparation section.

6. For cell and gene therapy products, according to the characteristics of the product, pharmaceutical research materials can be submitted in the corresponding part of the stock solution and/or preparation. For inapplicable items, "not applicable" can be indicated. For example, for the pharmaceutical research materials of plasmids and viral vectors in key raw materials, complete pharmaceutical research materials can be submitted in the "3.2.S.2.3 Material Control" section with reference to the requirements of CTD format and content. 7. When the applicant completes the clinical trial and submits the application for drug marketing registration, the applicant shall submit the clinical trial database in the form of a CD-ROM on the basis of the CTD. For specific requirements such as database format and related documents, please refer to the relevant guidelines for clinical trial data submission.

8. General or specific human immunity for intramuscular injection exempted from clinical trials according to regulations
Immune globulin, human albumin, etc., can directly submit a marketing application.

9. The application materials for in vivo diagnostic reagents of biological products shall be prepared in accordance with CTD.

Part III In Vitro Diagnostic Reagents Managed by Biological Products

1. Registration classification

Category 1: innovative in vitro diagnostic reagents.

Category 2: In vitro diagnostic reagents that have been marketed at home and abroad. 2. Application dossier requirements for in vitro diagnostic reagents can be directly submitted for marketing applications.

(1) Overview

1. Product name

2. Evidence documents 3. Description of patent status and ownership status Approved application materials (if applicable)

(2) Summary table of main research information

9. Basic product information 10. Summary of analysis performance information 11. Summary of clinical trial information (3) Research materials 12. Research materials of main raw materials 13. Research materials of main technological processes and test methods 14. Reference value (range) determination data 15. Analysis performance evaluation data 16. Stability study data

17. Manufacturing and verification records, production process (ie, manufacturing and verification procedures) 18. Clinical trial data III. Description of application materials

(1) Summary part

1. Product name: It can include common name, commodity name and English name at the same time. The generic name should conform to the relevant naming principles in the Chinese Pharmacopoeia.

2. Evidence documents: submitted in accordance with the "Guidelines for Acceptance and Review of In Vitro Diagnostic Reagents" Submit supporting documents.

3. A description of the patent status and its ownership status, as well as a statement that it does not infringe on the patents of others. 4. The basis and basis for the establishment of the title: including domestic and foreign research and development, production, use of the product and related literature. 5. Self-assessment report 5.1 Intended use of the product: the intended use of the product, the background of clinical indications related to the intended use, such as the incidence of clinical indications, susceptible populations, etc., relevant clinical or laboratory diagnostic methods, etc.

5.2 Product description: product name, packaging specifications, methods used, instruments used for testing, etc. Summary and evaluation of the main findings of the product. 5.3 Notes on biosafety: Since the main raw materials in in vitro diagnostic reagents may be prepared from various animals, pathogens, human tissues, body fluids or radioisotopes and other materials after processing or adding certain substances, in order to ensure For the safety of users and the environment during transportation and use, researchers should explain the protective measures adopted for the above-mentioned raw materials.

5.4 Others: Including the approval and listing of similar products at home and abroad. The technical methods and clinical application of related products, the products applied for registration are the same as those at home and abroad.

similarities and differences of products. For innovative diagnostic reagent products, literature on the relationship between the test substance and the intended clinical indication should be provided. The applicant should establish a scientific committee to conduct a comprehensive review of the variety development process and results to ensure the scientificity, integrity and authenticity of the data. Applicants should submit a self-examination report on research materials together. 6. Product specification and drafting instructions:

The product specification should meet the relevant requirements and

Prepared with reference to the relevant technical guidelines.

7. Packaging and label design samples: The label on the outer packaging of the product should include the generic name, the holder of the marketing license, the name of the manufacturer, the batch number of the product, and matters needing attention. The general name, commodity name and English name of the product can be marked at the same time. For various components in in

vitro diagnostic reagent products, such as calibrators, quality control products, cleaning solutions, etc., the Chinese name and batch number of the component should be marked on the packaging and label. If the components of the same batch number and different batch numbers cannot be replaced, not only the product batch number, but also the batch number of each component should be indicated. 8. Application materials for drug generic name approval (if applicable) (2) Summary of main research information

9. Basic product information: applicant, marketing authorization holder, production address, packaging address, etc. Test methods, testing instruments, etc. 10. Summary of analytical performance information: The main analytical performance indicators

include the minimum detection limit, analytical specificity, detection range, measurement accuracy (quantitative determination of products), intra-batch precision, inter-batch precision, storage conditions and validity period, etc.

11. Summary of clinical trial information: including clinical trial institutions, clinical research plans, total number of samples, number of clinical research samples in each clinical unit, sample information, clinical research results, other test methods used or basic information of other diagnostic reagent products, etc.

(3) Research materials 12.

Research materials on main raw materials

12.1 Radionuclide-labeled products: solid-phase carriers, antigens, antibodies, radionuclides, quality control substances, standards (calibrators) and corporate reference substances, etc. Research information on source, preparation and quality control should be provided. For quality control products, standard products (calibrators), and enterprise reference products, research data of quantification or traceability should also be provided.

12.2 Products based on immunological methods: solid-phase carriers, chromogenic systems, antigens, antibodies, quality control materials and corporate reference materials, etc., research data on sources, preparation and quality control should be provided. For quality control materials, standard materials (calibrators), and enterprise reference materials, research data for quantification or traceability should also be provided.

12.3 Nucleic acid detection kits for pathogenic microorganisms: primers, probes, enzymes, dNTPs, nucleic acid extraction and separation/purification systems, color development systems, quality control products, internal standards, and corporate reference materials, etc. Research data on source, preparation and quality control should be provided. For quality control products, internal standards, and enterprise reference products, test data of fixed value or traceability should also be provided. 13. Research data on main technological process and test methods 13.1 Radionuclide-labeled products: coating of solid-phase carrier, labeling of radionuclides, sample collection and processing, establishment of reaction system, research on quality control methods, etc. 13.2 Products based on immunological methods: including coating of solid-phase carriers, chromogenic systems,

Sample collection and processing, establishment of reaction systems, research on quality control methods, etc.

13.3 Pathogenic microorganism nucleic acid detection kit: sample processing, sample dosage, reagent dosage, nucleic acid separation/purification process, establishment of reaction system, research on quality control methods, and research on test methods for different models. 14. Reference value (range) determination data: Determination of negative samples, minimum detection limit samples, etc., and statistical analysis of the determination results to determine the reference value (range), indicating the power and confidence interval.

15. Analytical performance evaluation

data 15.1 Including minimum detection limit, analytical specificity (including choice of anticoagulant, internal

Items such as interference of source interfering substances, interference of related disease samples), detection range, measurement accuracy, intra-batch precision, inter-batch precision, and comparative research with approved registered products. For pathogenic microorganism nucleic acid detection products, the determination of domestic main subtype or genotype samples should also be considered. For the minimum detection limit, the power and confidence interval should be stated. 15.2 Multiple batches of products should be used for performance evaluation of the above items. Through statistical analysis of the performance evaluation results of multiple batches of products, product standards are formulated to effectively control the stability of product production processes and product quality. 15.3 If the registration application includes different packaging specifications, or the product is suitable for different models, it is necessary to use the product of each packaging specification, or to carry out the test data for the evaluation of the above items on different models. Different packaging specifications are only different in the amount of loading, so there is no need to provide the evaluation data for the above items. 15.4 For nucleic acid detection products of pathogenic microorganisms, if mixed samples are used for detection, the analytical performance of a single test sample and a mixed test sample should be evaluated separately.

15.5 State the quality standards and the basis for their determination. 16. Stability study data: including the stability study data of at least three batches of samples stored under actual storage conditions and open bottles until after the expiration date, and accelerated destructive test data should be provided if necessary.

17. Copies of manufacturing and verification records, manufacturing and verification procedures for at least three consecutive batches of product production and self-inspection records. Manufacturing and verification procedures: refer to the current edition of the Chinese Pharmacopoeia. 18. Clinical trial materials 18.1 Complete clinical trials in at least 3 domestic clinical institutions, and provide clinical trial protocols and clinical trial plans.

18.2 Provide a complete clinical trial report. 18.3 Detailed

information of clinical trials, including test data of all clinical samples, other test methods used or basic information of other diagnostic reagent products, such as test methods, sources of diagnostic reagent products, product instructions and registration and approval status, etc. 18.4 Total number of samples for clinical research: Radionuclide-labeled products:

at least 500 samples. Products based on immunological methods: at least 10,000 cases. Pathogenic microorganism

nucleic acid detection products: at least 100,000 cases. 18.5 When using the marketed products for comparative

research, the test results do not match the sample.

This needs to be further confirmed by using third-party products.

18.6 For pathogenic microorganism nucleic acid detection products: if mixed samples are used for detection Statistical analysis should be performed on the results of single-sample testing and mixed-sample testing respectively.

18.7 Overseas applicants should provide clinical trial data completed overseas, overseas clinical trials Summary report on bed usage and clinical trial data completed in China.

Attachment: M4: Regional Common Technical Document (CTD) for Human Drug Registration Application

information

attached

M4: Regional information on the Common Technical Document (CTD) for human drug registration applications

3.2.R Regional Information

3.2.R.1 Process Validation

Provide process validation protocols and reports.

3.2.R.2 Batch records When

applying for clinical trials, provide batch production and inspection records representing the sample process for clinical trials; when applying for marketing, provide key clinical representative batches and at least three consecutive batches to be listed.

Batch production and inspection records of municipal-scale verification

batches; and inspection reports for the above batches.

3.2.R.3 Analysis method validation report Provide

analysis method validation report, including typical graphs.

3.2.R.4 Stability Profile Provides a

profile typical of stability studies.

3.2.R.5 Comparable scheme (if applicable) 3.2.R.6 Other