Announcement of the China Food and Drug Administration on Issuing the Requirements for Application Data for the Registration of In-vitro Diagnosis Reagents and the Format of Approval and Supporting documents (No. 44 [2014])

Issued on September 5, 2014

Announcement of the China Food and Drug Administration

No. 44 [2014]

Announcement on Issuing the Requirements for Application Data for the Registration of In-Vitro Diagnosis Reagents and the Format of Approval and Supporting documents

To regulate the administration of the registration of in-vitro diagnosis reagents, and guide enterprises to properly perform registration application, the CFDA has organized the formulation of the requirements for application data for the registration of in-vitro diagnosis reagents and the format of approval and supporting documents (see Appendices 1-5) in accordance with the *Regulations on Supervision and Administration of Medical Devices* (No. 650 Decree of the State Council) and the *Administrative Measures for the Registration of In-vitro Diagnosis Reagents* (No. 5 Order of the China Food and Drug Administration), which are now issued for implementation on October 1, 2014.

It is hereby announced.

Appendices: 1. Medical Device Registration Certificate of the People's Republic of China (In-vitro Diagnosis Reagents) (Format)

2. Medical Device Registration Change Document of the People's Republic of China (In-vitro Diagnosis Reagents) (Format)

3. Requirements for and Description of Application Data for Registration of In-vitro Diagnosis Reagents

4. Requirements for and Description of Application Data for Extended Registration of In-vitro Diagnosis Reagents

5. Requirements for and Description of Application Data for Registration Change of In-vitro Diagnosis Reagents

China Food and Drug Administration
September 5, 2014

Appendix 1

Medical Device Registration Certificate of the People's Republic of China (In-vitro Diagnosis Reagents)

(Format)

No. of registration certificate:

Name of applicant	
Domicile of applicant	
Production address	
Name of agent	(Applicable to imported in-vitro diagnosis reagents)
Domicile of agent	(Applicable to imported in-vitro diagnosis reagents)
Product name	
Packaging specification	
Main ingredients	
Intended purpose	
Attachment	Technical requirements and instructions of the product
Storage conditions and effective period of the product	
Other contents	
Remarks	

Review and approval department: Date of approval: mm dd yyyy

Expiry date: mm dd yyyy

(Stamp of the review and approval department)

Appendix 2

Medical Device Registration Change Document of the People's Republic of China (In-vitro Diagnosis Reagents)

(Format)

No. of registration certificate:

Product name	
Changed content	"*** (original registration contents or items)" are changed to "*** (contents after change)".
Remarks	The document is used together with the " " registration certificate.

Review and approval department: Date of approval: mm dd yyyy

(Stamp of the review and approval department)

Appendix 3

Requirements for and Description of Application Data for Registration of In-vitro Diagnosis Reagents

	Class III products	Class II products
1. Application form	∨	∨
2. Supporting documents	∨	∨
3. Overview data	∨	∨
4. Study data on main raw materials	∨	△
5. Study data on main production process and reaction system	∨	△
6. Analytical performance evaluation data	∨	∨
7. Data on the determination of positive judgment value and reference range	∨	∨
8. Stability study data	∨	∨
9. Production and self-inspection records	∨	∨
10. Clinical evaluation data	∨	∨
11. Product risk analysis data	∨	∨
12. Product technical requirements	∨	∨
13. Product registration test report	∨	∨
14. Product instructions	∨	∨
15. Label sample	∨	∨
16. Compliance statement	∨	∨

Note: The applicant shall submit application data according to the requirements in the table above based on the product class.

∨: Data that must be provided.

△: Data not required for registration application which is kept by the applicant, but must be provided for technical review.

I. Application Form

II. Supporting Documents

(I) Domestic applicants shall submit: a copy of the Enterprise's Business License and a copy of the Certificate of Organization Code.

(II) Overseas applicants shall submit:

1. Supporting documents approving the marketing of the products and supporting documents proving the qualification to legally produce the products in application that are issued by the medical device authorities in the country (region) where the applicant is registered or the production address is located. If there is product class

description in such supporting documents, the class shall cover the products in application.

2. If the products are not managed as medical devices in the country (region) where the applicant is registered or the production address is located, the applicant shall provide relevant supporting documents, including supporting documents approving the marketing of such products in the country (region) where the applicant is registered or the production address is located.

3. Supporting documents proving that the applicant complies with the quality management system requirements in the country (region) where the applicant is registered or the production address is located or that the applicant has passed other quality management system certification.

4. Power of attorney of the agent designated by the applicant within the territory of China, the agent's Letter of Commitment, a copy of its Business License or a copy of its organization registration certificate.

III. Overview Data

(I) Intended purpose of the product. Describe the product's intended purpose, background information of clinical indications related to the intended purpose, such as the incidence of the clinical indications and susceptible groups, relevant clinical or laboratory diagnostic methods, etc..

(II) Product description. Describe the technical principle, sources and methods of preparation of main raw materials, the process of main production technology, methods of preparation of quality controls and calibrators and traceability (value setting) status.

(III) Description of biological safety. Since the main raw materials of in-vitro diagnosis reagents may be processed from various animals, pathogens, human tissues and fluids and other biological materials or prepared by adding certain substances, for human-derived materials, pathogen detection for infectious diseases (HIV, HBV, HCV, etc.) must be described and relevant supporting documents shall be provided. For other animal-derived materials and materials from microbial sources, the corresponding supporting documents shall be provided to prove that they are safe for the user and the environment during product transportation and use, and inactivation and other test methods adopted by the abovementioned raw materials shall be described.

(IV) Summary and evaluation of the main study results of relevant products.

(V) Others, including the approval status for marketing of products of the same kind at home and abroad, technical methods adopted by and clinical applications of relevant products, differences and similarities of the products in the application for registration and products of the same kind at home and abroad, etc. For newly developed in-vitro diagnosis reagent products, literature data on the relationship between the tested substance and the intended applicable clinical indications shall be provided.

IV. Study Data on Main Raw Materials

Study data on main raw materials include study data on the selection, preparation and quality standards of main reaction components, quality controls and calibrators, value

setting test data on quality controls and calibrators, calibrator traceability documents, etc.

V. Study Data on Main Production Technologies and Reaction Systems

Main production technologies include the preparation, sub-packaging and freeze-drying of working solution, coating and assembly of solid supports, description and basis for determination of color development/light emitting system, etc.; reaction systems include sample collection and handling, sample requirements, sample consumption, reagent consumption, reaction conditions, calibration method (if any), quality control methods, etc.

VI. Analytical Performance Evaluation Data

(I) Analytical performance evaluation of in-vitro diagnosis reagents mainly include precision, accuracy, sensitivity, specificity, linearity range or measurement range and other items. The performance of several batches of the product shall be evaluated, and the results shall be statistically analyzed in order to effectively control the stability of the production technology and product quality.

If the registration application includes different applicable models, test data on and summary of evaluation of the abovementioned items of different models shall be submitted.

If the registration application includes different packaging specifications, the differences among different packaging specifications shall be analyzed or verified. If there are performance differences among products of different packaging specifications, test data and summary on evaluation of the abovementioned items of products of each packaging specification shall be submitted. If there are no performance differences among different packaging specifications, a detailed explanation of no existence of performance differences shall be submitted, and the differences among different packaging specifications and their possible influences shall be specifically described.

(II) Complete traceability documents shall be submitted for calibrators.

(III) Value setting data on all applicable models shall be submitted for quality controls.

VII. Data on the Determination of Positive Judgment Value or Reference range

It is required to describe in detail the method or basis for the determination of positive judgment value or reference range, state the sources of samples adopted for the determination of positive judgment value or reference range, and provide detailed test data on and summary of the determination of positive judgment value or reference range.

For calibrators and quality controls, it is not required to submit data on the determination of positive judgment value or reference range.

VIII. Stability Study Data

Stability study data shall include the real-time stability study data on at least three batches of samples that have been preserved under actual storage conditions until after the effective period of the finished products, and corresponding stability studies shall be conducted with sufficient consideration of adverse conditions in the storage,

transportation and use of products. The basis for the determination of stability study methods and the specific test methods and processes shall be described in detail.

IX. Production and Self-inspection Records

A copy of the production and self-inspection records of three consecutive batches of products shall be provided.

X. Clinical Evaluation Data

(I) Clinical trial. For in-vitro diagnosis reagents requiring clinical trials, the applicant shall carry out clinical trials by referring to relevant technical guidelines, and provide the following clinical trial data:

1. Written comments of the Ethics Committee to approve the implementation of clinical trials.

2. Clinical trial protocol: the protocol shall be signed by the principal investigator, and stamped by the clinical trial institution undertaking each clinical trial, signed by the statistical person in charge and stamped by the unit, and stamped by the applicant.

3. Clinical trial report of each clinical trial institution: the clinical trial report of each clinical trial institution shall be signed and stamped by the clinical trial institution; the cover page of the report includes the generic name of the in-vitro diagnosis reagents used in the trial, start date and completion date of the trial, principal investigator (signature), trial institution (stamp), signature of the statistical person in charge and the unit (stamp), the applicant (stamp), contact person and contact information of the applicant, report date, and storage location of primary data.

4. Summary report on all clinical trial results: the summary report shall be completed by the leading unit of clinical trial institutions or the applicant, and the cover contents are the same as cover contents of the clinical trial report of each clinical trial institution.

5. Attachment to clinical trial reports: detailed data of the clinical trial, including other test methods adopted in the clinical trial and basic information of other diagnosis reagent products, such as test methods, source of diagnosis reagent products, product instructions and registration approval status, all test data in the clinical trial (which shall be signed by the clinical trial operator and reviewer, and stamped by the clinical trial institution), main references, resume of the principal investigator, other information to be explained by the applicant, etc.

(II) For products in the catalogue of in-vitro diagnosis reagents exempted from clinical trials issued by the China Food and Drug Administration, the corresponding clinical evaluation data shall be submitted, as well as data of evaluation of clinical performance in accordance with the corresponding guidelines (if any) by evaluating clinical samples covering the intended purpose and interference factors and combining with literature data, clinical empirical data and other product safety and effectiveness data, and information of sources of the clinical samples used.

(III) For imported products, summary report of clinical trial data completed overseas or overseas clinical applications shall also be submitted.

(IV) For calibrators and quality controls, it is not required to provide clinical trial data.

(V) The clinical trial institution's stamp mentioned in this chapter refers to the clinical trial institution's official seal.

XI. Product Risk Analysis Data

Risk analysis, risk evaluation and corresponding risk control shall be conducted in each process of the life time of in-vitro diagnosis reagent products based on the judgment of the intended purpose, possible use errors, safety-related characteristics, known and foreseeable hazards and other aspects and the evaluation of patient risks. On such basis, risk management reports shall be produced, which shall meet the requirements of the relevant industry standards.

XII. Product Technical Requirements

On the premise of stable raw material quality and production technology, the applicant shall compile product technical requirements based on the applicant's product development, previous clinical evaluation and other results in accordance with national standards, industry standards and relevant literatures. The contents mainly include the product's performance indicators and test methods. The technical requirements of Class III products shall define main raw materials, production technology and semi-finished product requirements in the form of appendices.

The product technical requirements of imported products shall include English version and Chinese version, the English version shall be signed and stamped by the applicant, and the Chinese version shall be signed and stamped by the applicant or its agent. The Chinese version of product technical requirements shall be made in two copies, and a statement on the complete consistency between the two copies of product technical requirements shall be submitted.

XIII. Product Registration Test reports

Such reports include registration test reports issued by medical device testing institutions with corresponding medical device testing qualifications and pre-evaluation comments on the product technical requirements. For products with national standards and references, registration tests shall be conducted with the national standards and references and shall comply with relevant requirements.

XIV. Product Instructions

For domestic products, the applicant shall formulate product instructions in accordance with the relevant requirements in the *Guidelines for the Drafting of Instructions of In-vitro Diagnosis Reagents* by referring to relevant technical guidelines.

For imported products, the applicant shall submit the original instructions approved or recognized by the overseas government authorities and its Chinese translation, and the agent shall formulate product instructions for use within the territory of China in accordance with the relevant requirements in the *Guidelines for the Drafting of Instructions of In-vitro Diagnosis Reagents* by referring to relevant technical guidelines.

Product instructions formulated according to the Guidelines shall be submitted in two copies, as well as a statement on the complete consistency between the two copies of the product instructions.

XV. Label Sample

It shall comply with the requirements in the *Provisions on the Management of Instructions and Labels of Medical Devices*.

The label of the external package of the product must include the product's generic name, applicant's name, production address, product batch number, precautions, storage conditions, effective period, etc.

For various components of in-vitro diagnosis reagent products, such as calibrators, quality controls and cleaning fluid, the label must specify the Chinese name and batch number of such components. If products of the same batch number and various components of different batch numbers cannot be replaced, the batch number of both the product and various components shall be specified.

For imported products, labels approved or recognized by overseas government authorities and their Chinese translation scripts shall be submitted, and the Chinese label sample shall be submitted according to the abovementioned requirements.

XVI. Compliance Statement

(I) The applicant states that the product complies with the *Administrative Measures for the Registration of In-vitro Diagnosis Reagents* and the requirements of relevant regulations, that the product's class complies with the requirements of *Administrative Measures for the Registration of In-vitro Diagnosis Reagents* and *Classification Sub-catalogue of In-vitro Diagnosis Reagents*, and that the product complies with currently effective national standards and industry standards, and provides a list of standards that the product complies with.

(II) Self guarantee statement for the authenticity of the data submitted (which shall be issued by the applicant for domestic products, and issued by the applicant and its agent respectively for imported products).

XVII. Other

In the application data for the registration of imported products, data No. III, IV, V,VI, VII, VIII, IX and XI shall be submitted by the applicant.

Appendix 4

Requirements for and Description of Application Data for Extended Registration of In-vitro Diagnosis Reagents

I. Application Form

II. Supporting Documents

Domestic applicants shall submit a copy of the Enterprise's Business License and a duplicate of the Certificate of Organization Code; overseas applicants shall submit Power of attorney of the agent designated by the applicant in China, the agent's Letter of Commitment, a copy of its Business License or a copy its organization registration certificate.

Note: For extended registration of imported medical devices, it is not required to provide supporting documents approving the marketing of the products in the country (region) where the applicant is registered or the production address is located.

III. Statement on No Change in the Product

The applicant shall provide a statement on no change in the product.

IV. A Copy of the Original Medical Device Registration Certificate and Its Attachment and a Copy of Previous Registration Change Documents of the Medical Device

V. Product Analysis Report within the Effective Period of Registration Certificate

(I) Clinical applications of the product, user complaints and measures taken.

(II) Summary, analysis and evaluation reports on medical device adverse events. The reports shall tabulate all suspected adverse events after marketing of medical devices, and describe the handling measures and solutions adopted by the manufacturer in each case. The reports shall also analyze and evaluate the abovementioned adverse events, elaborate on the cause of the adverse events, and describe their influences on safety and effectiveness.

(III) Market conditions of the product in all marketing countries and regions.

(IV) Product supervision and sampling inspection conditions (if any).

(V) If recall occurs after marketing, the reason for, process and handling result of the recall shall be described.

(VI) If the original medical device registration certificate expressly requires continued completion of the work, relevant summary reports shall be provided, and the corresponding data shall be attached.

VI. Product Test Report

If mandatory standards for the medical devices have been revised, product test reports proving that the product can meet the new requirements shall be provided. The product test report can be self-inspection report, commissioned test report or test report in line with the manufactory standards for implementing the provisions of circulars. In these reports, commissioned test reports shall be issued by medical device testing institutions with medical device testing qualifications.

If there are national standards and references released or updated, product test reports proving that the product complies with the requirements of such national standards and references shall be provided. The product test report can be self-inspection report, commissioned test report or test report in line with the provisions of corresponding circulars.

VII. Compliance Statement

(I) The applicant states that the product complies with the *Administrative Measures for the Registration of In-vitro Diagnosis Reagents* and the requirements of relevant regulations and that the product complies with currently effective national standards and industry standards, and provides a list of standards that the product complies with.

(II) Self guarantee statement for the authenticity of the data submitted (which shall be submitted by the applicant for domestic products, and submitted by the applicant and its agent respectively for imported products).

VIII. Others

In the event of changes involving the product instructions and/or product technical requirements during the effective period of the original registration certificate, two copies of the product instructions and/or product technical requirements that have been revised according to the registration change documents shall be submitted.

Appendix 5

Requirements for and Description of Application Data for Registration Change of In-vitro Diagnosis Reagents

Requirements for and Description of Application Data for Change of Registration Issues

I. Application Form

II. Supporting Documents

(I) Domestic applicants shall provide:

1. A copy of Enterprise's Business License.

2. A copy of the Certificate of Organization Code.

(II) Overseas applicants shall provide:

1. If the changed issues require obtaining of new supporting documents approving the marketing of the products and new supporting documents proving the enterprise's qualification issued by the medical device authorities in the country (region) where the applicant is registered or the production address is located, the corresponding documents shall be submitted; if the changed issues do not require approval from the medical device authorities in the country (region) where the applicant is registered or the production address is located, it shall be explained.

2. Power of attorney of the agent designated by the overseas applicant within the territory of China, the agent's Letter of Commitment, a copy of its Business License or a copy of its organization registration certificate.

III. Applicant's Statement on the Changes

IV. A Copy of the Original Medical Device Registration Certificate and Its Attachment and a Copy of Previous Registration Change Documents of the Medical Device

V. Requirements for Change-related Application Data

(I) Change of the applicant's name:

Approval notice for enterprise name change (domestic applicants) and/or a description of the detailed changes and the corresponding supporting documents.

(II) Change of the applicant's domicile:

A description of the detailed changes and the corresponding supporting documents.

(III) Change of production address of domestic in-vitro diagnosis reagents:

Product License after the corresponding change shall be provided.

(IV) Change of the agent:

1. Statement on change of the agent issued by the applicant.

2. Power of attorney for the new agent issued by the applicant, and Letter of Commitment issued by the new agent.

3. A copy of the Business License or a copy of the organization registration certificate of the agent after the change.

(V) Change of the agent's domicile:

A copy of the Business License or a copy of the organization registration certificate before and after the change.

VI. Compliance Statement

(I) The applicant states that the product complies with the *Administrative Measures for the Registration of In-vitro Diagnosis Reagents* and the requirements of relevant regulations and that the product complies with currently effective national standards and industry standards, and provides a list of standards that the product complies with.

(II) Self guarantee statement for the authenticity of the data submitted (which shall be submitted by the applicant for domestic products, and submitted by the applicant and its agent respectively for imported products).

Requirements for and Description of Application Data for Change of License Issues

I. Application form

II. Supporting documents

(I) Domestic applicants shall provide:

1. A copy of the Enterprise's Business License.

2. A copy of the Certificate of Organization Code.

(II) Overseas applicants shall provide:

1. If the changed issues require obtaining of new supporting documents approving the marketing of the products and new supporting documents proving the enterprise's qualification issued by the medical device authorities in the country (region) where the overseas applicant is registered or the production address is located, the corresponding documents shall be submitted; if the changed issues do not require approval from the medical device authorities in the country (region) where the applicant is registered or the production address is located, they shall be explained.

2. Power of attorney of the agent designated by the overseas applicant within the territory of China, the agent's Letter of Commitment, a copy of its Business License or a copy of its organization registration certificate.

III. Applicant's Statement on the Changes

(I) Reasons for and purpose of the changes.

(II) Technical analysis on the influences that the changes may cast on the product's performance.

(III) Product risk analysis data related to the product's changes.

IV. A Copy of the Original Medical Device Registration Certificate and Its Attachment and a Copy of Previous Registration Change Documents of the Medical Device

V. Requirements for Other Technical Data on the Specific Changes

(I) For the change of suppliers of antigen, antibody and other main materials, the following data shall be submitted:

1. Study data on antigen, antibody and other main materials after the change.

2. Analytical performance evaluation data.

3. Clinical trial data.

4. Product technical requirements and product instructions before and after the change.

(II) For the change of testing conditions, positive judgment value or reference range, the following data shall be submitted:

1. Definite detailed test data on testing conditions, positive judgment value or reference range after the change.

2. Clinical trial data.

3. Product technical requirements and product instructions before and after the change.

(III) For the change of the product storage conditions and/or effective period, the following data shall be submitted:

1. Test data on product stability study.

2. Product technical requirements, product instructions and label sample before and after the change.

(IV) For changes modifying the product technical requirements without lowering the product's effectiveness, the following data shall be submitted:

1. Test data on analytical performance evaluation.

2. Product technical requirements and product instructions before and after the change.

(V) For the change of the production address of imported in-vitro diagnosis reagents, the following data shall be submitted:

1. Quality system assessment report on the change of the production address of imported in-vitro diagnosis reagents (if any).

2. Supporting documents proving that the new production site complies with the quality management system requirements in the country (region) where the

production address is located or that it has passed other quality management system certification.

3. Test data on analytical performance evaluation of products manufactured after the adoption of the new production site.

4. Product instructions and label sample after the change.

(VI) For modifications of wording in the product instructions and/or product technical requirements without involving changes of technical contents, the following data shall be submitted:

1. A description of changes of the product instructions and/or product technical requirements, in which a comparison table of the changes shall be included.

2. Product instructions and/or product technical requirements before and after the change.

(VII) For the change of packaging specifications, the following data shall be submitted:

1. Product technical requirements, product instructions and label sample (if involved) before and after the change.

2. After judgement on whether there are performance differences between the changed packaging specification and the marketed packaging specification, if there are differences in product performance, then test data on analytical performance evaluation of products with the changed packaging specification shall be provided; if there are no differences in product performance, a detailed explanation for no existence of performance difference between the changed packaging specification and the marketed packaging specification shall be provided to specifically describe the differences among different packaging specifications and their possible influences.

(VIII) For the change of applicable models, the following data shall be submitted:

1. Test data on analytical performance evaluation by adopting the new model.

2. Product technical requirements, product instructions and label sample (if involved) before and after the change shall be provided.
(IX) For changes increasing the clinical indications, the following data shall be submitted:

1. Analytical performance evaluation data on the increased clinical indications (if involved).

2. Clinical trial data on the increased clinical indications.

3. Product technical requirements and product instructions before and after the change.

(X) For changes increasing the sample types for clinical test, the following data shall be submitted:

1. Clinical trial data on comparison of the increased sample types for clinical test and approved sample types. If the increased sample types have no direct comparability with the originally approved sample types, marketed products of the same kind comparable to the sample types may be selected for comparative clinical trials.

2. Product technical requirements and product instructions before and after the change.

(XI) For other changes that may affect the product's effectiveness, test data on relevant changes shall be provided based on the specific changes.

(VII) Test data on verification of possible influences that may be cast by the changes on the product's performance shall be provided based on the product's specific changes (if involved).

VI. Compliance Statement

(I) The applicant states that the product complies with the *Administrative Measures for the Registration of In-vitro Diagnosis Reagents* and the requirements of relevant regulations and that the product complies with currently effective national standards and industry standards, and provides a list of standards that the product complies with.

(II) Self guarantee statement for the authenticity of the data submitted (which shall be submitted by the applicant for domestic products, and submitted by the applicant and its agent respectively for imported products).