

Provisional Translation (as of March 2020)*

PFSB/ELD/OMDE Notification No. 1121-16

November 21, 2014

To: Commissioner of the Prefectural Health Department (Bureau)

Counsellor of Minister's Secretariat, Ministry of Health, Labour and Welfare
(Evaluation and Licensing of Medical Device/Cellular and Tissue-based Products)
(Official seal omitted)

Points to Consider When Applying for Marketing Approval of *In Vitro* Diagnostics

The handling of applications for marketing approval of *in vitro* diagnostics is described in "Points to Consider When Applying for Marketing Approval of *In Vitro* Diagnostics" (PFSB/ELD/OMDE Notification No. 0216005, dated February 16, 2005, by the Director of the Office of Medical Device Evaluation, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare [MHLW]; hereinafter referred to as the Former Notification), etc.

The handling of applications, etc. for marketing approval of *in vitro* diagnostics pursuant to the provisions in Article 23-2-5, Paragraph 1 and Article 23-2-17, Paragraph 1 of the "Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics" (Act No. 145 of 1960; hereinafter referred to as the Act) as revised pursuant to the provisions in the "Act for Partial Amendment of the Pharmaceutical Affairs Act" (Act No. 84 of 2013), was notified in the "Application for Marketing Approval of *In Vitro* Diagnostics" (PFSB Notification No. 1121-15, dated November 21, 2014, by the Director of the Pharmaceutical and Food Safety Bureau, MHLW; hereinafter referred to as the Director's Notification). We have decided on the details of handling, etc. as provided below. You are therefore requested to review the information below, and notify all relevant associations, organizations and other parties under your jurisdiction of the information.

The Former Notification will be abolished upon application of this Notification on November 25, 2014.

* This English version of the Japanese Notification is provided for reference purposes only. In the event of any inconsistency between the Japanese original and the English translation, the former shall prevail.

Copies of this Notification will be sent to the Chief Executive of the Pharmaceuticals and Medical Devices Agency (PMDA); the President of the Federation of Pharmaceutical Manufacturers' Associations of Japan; the President of the Japan Association of Clinical Reagents Industries; the Chairman of the American Medical Devices and Diagnostics Manufacturers' Association; the Chairman of the Medical Equipment & Diagnostics Committee of the European Business Council in Japan; and the Chairman of the Association of Registered Certification Bodies under the Pharmaceutical Affairs Act.

Chapter I Descriptions in the Application Form for Marketing Approval

Each section of the application form for marketing approval of *in vitro* diagnostics should be completed in accordance with the instructions described below and other separately specified instructions. The term “Enforcement Ordinance” refers to the “Ministerial Ordinance for Enforcement of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics” (Ministry of Health and Welfare [MHW] Ordinance No. 1 of 1961) as revised pursuant to the provisions in the “Ministerial Ordinance on Arrangement of Relevant Ministerial Ordinances Incidental to Enforcement of the Act for Partial Amendment of the Pharmaceutical Affairs Act and to Enforcement of Cabinet Order on Arrangement etc. of Relevant Cabinet Orders and Interim Measures Incidental to Enforcement of the Act for Partial Amendment of the Pharmaceutical Affairs Act” (MHLW Ordinance No. 87 of 2014). The term “Essential Standards” refer to the “Standards of *In Vitro* Diagnostics Defined by the Minister of Health, Labour and Welfare pursuant to the Provisions in Article 41, Paragraph 3 of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics” (MHLW Ministerial Announcement No. 126 of 2005) as revised pursuant to the provisions in the “Partial Revision of the Standards of *In Vitro* Diagnostics Defined by the Minister of Health, Labour and Welfare Pursuant to the Provisions in Article 42, Paragraph 1 of the Pharmaceutical Affairs Act” (MHLW Ministerial Announcement No. 402 of 2014). The term “approval standards” refer to the standards of *in vitro* diagnostics required to undergo a regulatory review that examines their conformity to the standards stipulated in the “Establishment of Approval Standards of *In Vitro* Diagnostics” (PFSB Notification No. 0622006, dated June 22, 2005, by the Director of the Pharmaceutical and Food Safety Bureau, MHLW). If MHLW issues other Notifications that provide new instructions, please complete the application form in accordance with the instructions.

1. Name

(1) Generic name

- 1) Provide the generic name and classification code number of the proposed *in vitro* diagnostic product as defined in the “Generic Names of *In Vitro* Diagnostics” (PFSB Notification No. 0401031, dated April 1, 2005, by the Director of the Pharmaceutical and Food Safety Bureau, MHLW).

Leave this column blank if there is no applicable generic name for the proposed *in vitro* diagnostic product at the time of submission. The product will be given an appropriate generic name by the time of approval. In such a case, provide a summary of the product in the “Remarks” column. (The summary must describe what is measured/detected by the product and the clinical significance of the product in approximately 300 characters in Japanese).

- 2) If a single product can carry out several different measurements simultaneously, provide all the relevant generic names and classification code numbers.
- 3) If the applicant intends to apply for approval of a product series, provide the generic name and classification code number of the product series.

(2) Brand name

Marketing authorization holders (MAHs) are free to give a brand name to their *in vitro* diagnostic products, in principle. However, avoid a name that may cause misunderstanding or confusion among users, or a name that degrades or exaggerates the concerned *in vitro* diagnostic product. Points of concern are provided below for reference.

- 1) Avoid a name that is already commonly used. If a commonly used name is selected, the company name or its abbreviation should be given before or after the name, to ensure that it can be distinguished from similar products of other companies.
- 2) Avoid a name comprised only or mostly of English alphabet (or a combination of English alphabet, numbers, and symbols). It is, however, acceptable to use English words that are commonly used in medical practice of Japan (e.g., those used in the list of medical fee points). In such a case, use a name that is distinguishable from those of similar products of other companies, as stated in the above paragraph 1).
- 3) Two or more variables can be submitted as a single product as long as they share the same reactive ingredient (i.e., the ingredient described in the “Reactive ingredients” column) even if they contain different non-reactive ingredients, such as preservatives and surfactants. Further, two or more variables containing different quantities of the same reactive ingredient can

be submitted as a single product if each quantity is within the range specified by the applicant.

- 4) A single product should be given only one brand name, in principle. However, if the applicant seeks approval of a product under more than one brand name on reasonable grounds, it must submit a document explaining the reason, together with the application form. In such a case, submit separate application forms for each brand name.

2. Intended Use

State the target analyte (type of specimen), measurement/detection properties, and classification (i.e., detection or measurement) of the proposed product. Indicate the clinical significance of the product by stating, for example, “measurement of ○○ in serum for △△ infection” or “measurement of ○○○ in serum (an aid for diagnosis of △△).” If the applicant intends to add a new clinical significance and/or to add target analyte to an approved product, it must submit a partial change approval application to change the intended use of the product.

If an abbreviation etc. is used to mean a target analyte, provide its official name as well since use of the abbreviation may cause misunderstanding. Refer to terms used in the list of the medical fee points, if available.

Use the wording “detection of ○○○” for qualitative testing and “measurement of ○○○” for quantitative and semi-quantitative testing. When the type of specimen is described as “in blood” in health insurance coverage classification, it should be clarified by stating “in whole blood,” “in plasma” or “in serum” according to the performance of the products.

If a product measures several types of specimens, use the wording “measurement of ○○ in serum or plasma” and the like.

If a product is used for both detection and measurement, use the wording “detection or measurement of ○○○.”

3. Shape, Structure, and Principle

Provide a brief summary describing the proposed product to facilitate the understanding of its characteristics.

(1) Constituent reagent(s)

- 1) Provide the name of the constituent reagent(s).
- 2) State the form of the reagent(s) if the shape or structure does not affect the performance.
- 3) If there are several standard solutions, attach a number (1, 2, or 3) or symbol (A, B, or C) to each solution, instead of merely stating “standard solutions,” to clearly indicate that there are two or more standard solutions.

(2) Shape

Provide a figure showing the shape and structure of the product if they affect the performance. The figure must clearly show the sample port, result window, etc. The size of the product need not be specified if it does not affect the performance.

(3) Principle

Describe the principle of how reactive ingredient(s) react and measure/detect the target properties. In principle, an ingredient is classified as reactive if it is thought to be reactant of the major reaction scheme of the test.

If the measurement/detection principle is known to those skilled in art and technical terms are used by scientific societies, etc., it is acceptable to use such terms to describe the principle.

4. Reactive Ingredient(s)

Provide the name of all constituent reagent(s). For the reactive reagent(s) also provide the name and quantity of the reactive ingredient(s) contained in it (them). The quantity may be given per bottle or per measurement unit (per measurement or per 10 measurements).

If the accurate quantity per test cannot be measured (e.g., antibodies in a solid-phase well or bead plate), use wording such as “one well per test” and state the total quantity of the ingredient. For example, if a well plate has 96 wells, specify the total quantity of the ingredient that can be contained in the whole 96-well plate. Further, describe procedures for controlling the content of constituent reagent(s) as supplementary information. For

example, wording such as “antibody levels between ○○ and ○○ of absorbance” is acceptable.

- 1) The quantity or content of reactive ingredients may be expressed as a range whose successful performance has been validated.
- 2) Two or more variables containing different quantities or contents of the same reactive ingredient can be submitted as a single product if each quantity or content is within the range specified by the applicant. Further, two or more variables can be submitted as a single product as long as they have the same performance even if they contain different non-reactive ingredients, such as preservatives.
- 3) The quantities of some reactive ingredients are expressed in units (e.g., “U” for enzyme levels). If the standards for an ingredient are listed in compendial documents such as the International System of Units, Japanese Pharmacopoeia, Japan Industrial Standard (JIS), use the standard unit provided in the documents.

If the applicant has newly established a unit, provide an explanation of the unit. If the constituent reagent is a lyophilized product, the quantities of ingredients may be expressed as in-use concentrations as long as the description is accompanied by a statement indicating that the quantities are given in in-use concentrations.

- 4) For animal-derived antibodies (antiserum), state the animal species in *katakana* (a Japanese syllabary). If applicable, state the name of cells producing monoclonal antibodies. Specify whether the antibodies are monoclonal or polyclonal antibodies.
- 5) If the test involves nucleic acid amplification, describe the nucleotide sequence of the probe to be used (the probe must guarantee the specificity of the reaction).
- 6) If the name of an ingredient is very long, a shortened name (i.e., an abbreviation or trivial name) may be used if it is widely used in general medical and pharmaceutical articles, etc. or in academic presentations, and is therefore unlikely to cause misunderstanding among users. In this case, give the official name along with the abbreviation or trivial name.

5. Product Specifications

State the measurement range or detection sensitivity as the method of quality control of the finished product and as an example thereof.

(1) Method of quality control

Describe the performance of the finished product as a kit, in view of the characteristics of the *in vitro* diagnostics. Set the following specifications, for example.

Quality control specifications are not limited to the test attributes listed below, but should include, as necessary, other test attributes. If the specifications include test attribute(s) other than those listed below, provide the rationale for selecting them.

1) Sensitivity

This defines the ability to detect and/or identify the target analyte or to measure the quantity and/or step values of the target analyte.

2) Accuracy

This defines the accuracy of the detection/identification results or measurements, etc.

3) Within-run reproducibility

This defines the reproducibility (degree of variability) of results when a single specimen is measured/detected simultaneously several times.

Consider the following points when selecting test attributes.

- a. If a measurement instrument is used, specific acceptance criteria should be established after giving due consideration to the performance of the measurement instrument and the testing conditions.
- b. If a single product is used to test two or more types of specimens (e.g., serum and urine), it is allowed to describe test attributes of only one of the specimens as long as the product ensures the same performance across the specimens. If the performance varies among the specimens, describe test attributes of all of the specimens.
- c. A test attribute may be omitted if it is deemed clearly unnecessary on reasonable grounds, in view of the characteristics of the *in vitro* diagnostics.
- d. Describe reference materials (including their origin) used in the above tests for quality control.

(2) Measurement range (detection sensitivity)

If the product is intended to measure an analyte(s), describe the measurement range when a representative instrument (or the dedicated instrument, if any) is used. If the product is intended to detect an analyte(s), describe the minimum detection sensitivity.

6. Directions for Use

Provide a brief summary of how to prepare the reagent and test solution and how to operate them separately, to ensure that users can understand the summary of how to use the product. Describe the specimen collection procedures or storage conditions if they affect measurement results and therefore require special attention.

- (1) If a measurement instrument is used, provide the general term of the instrument (e.g., spectrophotometer, automated blood analyzer, blood cell counter), and describe its standard operating procedure. If measurement is performed using an instrument, the necessary operating procedures should not be described from the standpoint of the instrument, but from the standpoint of the reagent. If the reagent is used with a dedicated instrument, provide the name of the instrument.
- (2) State the preparation method of the reagent and test solution. If the reagent or test solution is used without preparation, state “the reagent (test solution) will be used without preparation” instead of simply writing “None” in the column.

When describing a reagent preparation method, it is acceptable to use the wording “The prescribed amount of ingredients is added to obtain the target concentration,” instead of precisely specifying the amount of the ingredients.

- (3) Specify the quantity of the specimen and reagent. The quantity may be expressed in a range like “○○ μL to ○○ μL,” or the ratio of fluid volume like “to 1 volume of specimen, add 3-5 volumes of the first reagent and 2 to 4 volumes of the second reagent.”
- (4) Specify the wavelength to be used. If the reagent is not used with a single dedicated instrument but with several types of instruments, and wavelength differs between the instruments, the wavelength may be expressed in a range that has previously been validated for measurement with the instruments. Even in this case, do not use phrases such as “specific wavelength” or “certain (given) wavelength,” but specify the wavelength or provide its range in an understandable way.

- (5) A reagent of the same formulation may be available in both a manual kit and an automated analyzer kit. If the two kits have different names, they must be handled as separate products. If the kits have the same name, they can be submitted for approval as a single product; in this case, describe how to use each kit separately in the “Directions for use” column.
- (6) A single product may be used for both qualitative and quantitative (or semi-quantitative) tests. In this case, the directions for use for qualitative and quantitative tests, if they differ, must be described separately.
- (7) State the clinical cutoff, etc. for qualitative parameters.
- (8) Describe separately the operating procedure for manual, automated analyzer, or the combination of the two.

7. Manufacturing Method

- (1) Describe the manufacturing method of each constituent reagent of an *in vitro* diagnostic product, in reference to Appendix 1. If any of the constituent reagents are distributed as a single product for refilling, provide a statement to that effect.
- (2) Provide easy-to-understand information on the registered manufacturing sites for each manufacturing process, in reference to Appendix 1. This should contain information on registered manufacturing sites involved in the processes of designing of the *in vitro* diagnostic product, filling of the reactive ingredient(s) in the final container, and storage of the finished product in Japan, as provided in the “Handling of Manufacturing Business for Medical Devices and *In Vitro* Diagnostics” (PFSB/ELD/OMDE Notification No. 1003-1, dated October 3, 2014, by the Counsellor of Minister’s Secretariat [for Evaluation and Licensing of Medical Device/Cellular and Tissue-based Products], MHLW). For radiation-emitting *in vitro* diagnostics, describe all registered manufacturing sites involved in the processes of designing of the product, filling of the reactive ingredient(s) in the final container, and storage of the finished product in Japan before release. It is, in principle, not required to give descriptions of each process or flowcharts of the processes if misunderstanding of the relationship between each process is unlikely to occur (e.g., in case where all processes are performed at a single registered manufacturing site). However, if the manufacturing process is complicated, the relationship should be appropriately described using flowcharts, as necessary.

- (3) If a proposed product incorporates another *in vitro* diagnostic product that has been approved or certified or submitted for marketing notification, the applicant must provide the name of the MAH of the incorporated product, its principal place of business and MAH license number, and the approval/certification/notification number of the incorporated product.
- (4) If the drug substance of a proposed product is registered in the drug master file pursuant to Article 80-6, Paragraph 1 of the Act (hereinafter referred to as the drug master file registration), provide the following information in the section of the manufacturing site of the drug substance: the name and address of the MAH, the name and address of the manufacturing site, and the registration number and date of the drug master file. If the manufacturing site is required to obtain a drug manufacturing license, state the license category, license number, and license date. If the manufacturing site is required to obtain an *in vitro* diagnostic manufacturing registration, state the registration number and registration date. If the manufacturing site is currently applying for a manufacturing license (certification) or registration, provide a statement to that effect.
- (5) A group consisting of two or more relevant *in vitro* diagnostic products can be submitted for approval as a single product series for multiple use. If a product series is submitted for approval, provide the details of constituent products for each category of approval, certification, and notification.

8. Storage Conditions and Shelf Life

Set the most appropriate storage conditions based on the stability test results. If a decrease in performance over a long period of time cannot be prevented, specify the shelf life to guarantee durable performance for use as an *in vitro* diagnostic product.

Essentially, the applicant is required to conduct necessary studies to guarantee the performance of the *in vitro* diagnostic product in view of the change in the product over time, and then fully examine and set the appropriate storage conditions and shelf life. The following points should also be considered.

- (1) Leave the column blank when the product has been stable at room temperature for 3 years or longer. If the duration of stability at room temperature is less than 3 years, state the shelf life only; if the duration of stability at other conditions than room temperature is 3 years or longer, state the storage conditions only.

- (2) Set the shelf life in view of the characteristics of the product and its distribution period. It is accepted to set a shorter shelf life than that of existing products if it does not interfere with its use and distribution.
- (3) Storage conditions and shelf life may vary between different constituent reagents. In this case, the bottle label etc. of each reagent may display its own storage condition and shelf life, different from those of other reagents, provided that the different storage conditions and shelf lives are described separately in the “Storage Conditions and Shelf Life” column. Even in such a case, the applicant is required to set storage conditions and a shelf life of the kit itself, as far as possible.

9. Manufacturing Sites of the Product Intended for Marketing

In reference to Appendix 2, provide the name of the manufacturing site, its registration number, and the manufacturing procedure of the following manufacturing processes: designing of the product; filling of the reactive ingredient(s) in the final container; and storage of the finished product in Japan. For radiation-emitting *in vitro* diagnostics, describe all registered manufacturing sites involved in the processes of designing of the product, filling of the reactive ingredient(s) in the final container, and storage of the finished product in Japan before release.

10. Remarks

- (1) State the license date, license category, and license number of the MAH, and the address of the principal place of business. If the license is under application, provide a statement to that effect (including the address of the principal place of business).
- (2) Indicate the approval application category of the product, namely, novel products, products without approval standards, products with approval standards, or products without conformity to standards.
- (3) If there is no applicable generic name for the *in vitro* diagnostic product at the time submission of the application, provide a summary of the product. (The summary must summarize the measurement/detection target properties and describe clinical significance of the product in approximately 300 characters in Japanese.)
- (4) If a product submitted for marketing approval does not meet the approval standards, standards of waiver of approval or certification pursuant to Article 23-2-5,

Paragraph 1 of the Act, or certification standards pursuant to Article 23-2-23, Paragraph 1 of the Act, explain the reason for the nonconformity to the relevant standards.

- (5) If the application is for a product series, provide a statement to that effect and the reason for submitting a product series application.
- (6) If the application is for a radiation-emitting *in vitro* diagnostic product, provide a statement to that effect.
- (7) If the application is for a product that must undergo a pre-approval study, provide a statement to that effect.
- (8) If the application is for an *in vitro* diagnostic product manufactured using recombinant technology, state that recombinant technology is used for manufacture.
- (9) If the product is accompanied by any accessories, provide a statement to that effect and describe the details of the accessories.
- (10) Attach the package insert (draft).
- (11) If the shape and structure of the proposed product are illustrated with a diagram(s) in the “Shape, structure, and principle” column, attach a photograph(s) showing the appearance of the product.
- (12) Indicate whether the product is subject to a QMS inspection. If the product undergoes the inspection, indicate where to submit the application for the inspection by providing the name of the organization (PMDA or a registered certification body) that will receive the application. If a QMS inspection is omitted, provide the rationale for the omission, write the number of the valid certificate of conformity to the standards and the date of its issuance, and attach a copy of the certificate.
- (13) Indicate whether the applicant requests health insurance coverage of the product and, if it requests the coverage, state the category insurance.
- (14) State, if applicable, that the application is for an *in vitro* diagnostic product that falls within the scope of “Points to Consider When Applying for Marketing Approval for Companion Diagnostics, etc. and Related Drugs” (PFSB/ELD Notification No. 0701-10, dated July 1, 2013, by the Director of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW). If applications for both the companion diagnostic product, etc. and its related drug are submitted for approval at the same time, provide a statement to that effect.

Chapter II Handling of Applications for Product Series

If a product series is submitted for approval, complete the Constituent Product Data Sheet (see Attached Form) separately for each constituent product.

Chapter III Data Submitted with the Application Form for Marketing Approval of *In Vitro* Diagnostics

1. Studies that provide data to be submitted with the application form for marketing approval must be conducted properly by experienced investigators at well-equipped facilities based on the academic standards of medicine, pharmacology, etc. at that point in time.
2. Data submitted with the application form for marketing approval must be written in Japanese. However, this shall not apply to literature, etc. used for reference. If these data are not written in Japanese, attach a summary translation. In this case, the untranslated original text should also be submitted.
3. Provisions in each of Item 2, Paragraph 1, Article 114 of the Enforcement Ordinance shall generally refer to the data listed in the right columns of Attached Table 1 of the Director's Notification.
4. Data submitted with the application form for marketing approval should, in principle, include the data listed in Attachment Table 2 of the Director's Notification. See the right columns for data classification.

Some studies may be considered unnecessary based on the characteristics, etc. of the *in vitro* diagnostic product. Data relating such studies may be omitted.

5. Outline of data submitted with the application form for marketing approval
 - A. History of Development and Status of Use in Foreign Countries, etc.
 1. History of development and Status of use in foreign countries, etc

Describe the history of development, use in Japan and foreign countries, and clinical diagnostic significance of the product.

2. Description of the product submitted for registration

Briefly explain the novelty or characteristics, etc. of the product for each of the following items.

- Measurement/detection method (measurement/detection principle, operating procedure [including how to judge the results])
- Information on the reactive ingredient(s)
- Explanation of the similarity between the proposed product and existing *in vitro* diagnostic products (if the product is not classified as a novel product, provide a statement to that effect).

B. Setting of Specifications

1. Method of quality control

- Prepare data on measurements obtained by the tests included in the proposed quality control specifications. Each test must be conducted on at least three batches, and each batch must be tested at least three times. Measurements obtained in this way must be included in the data.
- Quality control specifications should include test attributes necessary to guarantee the quality and performance of the product (e.g., the test attributes (a) to (c) listed below). If the specifications include test attributes other than (a) to (c), provide the rationale for selecting them.
 - (a) Sensitivity
 - (b) Accuracy
 - (c) Within-run reproducibility
- For *in vitro* diagnostic products using an antigen-antibody reaction:
If the strain of the antibody-producing cells is planned to be changed, provide procedure of tests to evaluate the equivalence on performance after the change and explain the rationale for procedure of the tests.

2. Measurement range, etc.

- For a reagent for measurement, state the measurement range (upper and lower limits) and, in principle, the minimum detection sensitivity.

- For a reagent for detection, provide the test results of the minimum detection sensitivity.
3. Reference materials for calibration
- State the details of the primary reference material for calibration (including its origin), rationale for selecting the material, and the material's composition, purity, and concentration or potency.
- C. Stability
- Storage conditions and shelf life
- Set the shelf life with due consideration to the characteristics of the kit and its distribution period.
 - The stability tests included in the quality control specifications must be conducted until the end of shelf life under the specified storage conditions.
 - Each test must be conducted on at least three batches. Each batch must undergo the same test at ≥ 3 time points including baseline, and must be tested at least twice per time point. Test results obtained in this way must be included in the data.
- D. Conformity to the Standards Stipulated in Article 41, Paragraph 3 of the Act
- Conformity to Essential Principles
- Declaration of conformity to Essential Principles

If the applicant intends to claim that the proposed *in vitro* diagnostic product conforms to Essential Principles and approval standards, if any, relevant to the product, attach a declaration stating that the product conforms to the approval standards and that the product is manufactured in conformity to Ministerial Ordinance on Quality Management System for Medical Devices and *In Vitro* Diagnostics (MHLW Ministerial Ordinance No.169 of 2004). The declaration of conformity should be prepared in accordance with ISO 17050-1 “Conformity Assessment - Supplier’s Declaration of Conformity Part 1: General Requirement).
 - Conformity to Essential Principles

Submit a document showing the conformity to Essential Principles; it must be prepared by going through the checklist for conformity to Essential Principles.

Alternatively, submit a list of the standards, criteria, tests, etc. that have been used to guarantee the conformity of the *in vitro* diagnostic product to Essential Principles, and also the test results showing the conformity to the standards and criteria used.

Appropriate standards or criteria may be unavailable for some *in vitro* diagnostic products, but there may be standards or laws and regulations that can be used for reference. In such a case, the applicant may be permitted to conduct required studies according to the reference standards in order to demonstrate the conformity to Essential Principles. If the applicant conducts studies in this manner, it must explain the rationale for conducting the studies.

E. Performance

1. Performance

- Spike-and-recovery testing

Conduct this testing as necessary if the product is intended for measurement and if a solution containing the target analyte at a specified concentration can be prepared using a material whose concentration has been measured by a validated authorized method.

- Dilution testing

Conduct this testing to confirm the linearity, etc. of the calibration curve if the product is intended for measurement.

2. Method of operation

- Provide the study results of important reaction conditions (reaction time, etc.) for the product requiring manual operation.
- If special caution needs to be exercised when collecting specimen, provide data supporting the necessity of the caution.

3. Specimens

- Submit data on reaction specificity (effect of coexisting materials, cross reactivity, nonspecific reactions, effect of inactivation, effect of anticoagulants, etc.), as necessary.

4. Correlation with approved *in vitro* diagnostics

- If the proposed product is classified as a product with approval standards, prepare data on correlation with approved *in vitro* diagnostics by referring to the notifications on approval standards.
- If the application is filed in a category of products without approval standards or products without conformity to standards, and performance, etc. of the *in vitro* diagnostic product are explained based on correlation with approved *in vitro* diagnostics, prepare data on the correlation, in reference to the notifications related to the approval standards.

5. Studies using seroconversion panels, etc.

- If seroconversion panels, etc. are available and their assessment is deemed necessary, submit the relevant study results.

F. Risk Management

Risk management system and important hazards

- Submit data on the in-house risk management system and overview of its implementation status for the proposed *in-vitro* diagnostic product, in reference to JIST14971 “Medical Devices - Application of Risk Management to Medical Devices.” In the risk analysis, explain that the foreseeable risks are acceptable in relation to the clinical efficacy of the product.
- The applicant may be requested by MHLW, etc. to provide safety measures against some of the potential hazards associated with the proposed product. If there are such hazards, submit tabulated data summarizing the risk analysis results and risk mitigation activities that have been undertaken to deal with the hazards.
- In addition to the above, if serious hazards are found as a result of risk analysis based on JIST14971, submit tabulated data summarizing the risk analysis results and risk mitigation activities concerning the hazards.
- Ingredients contained in constituent reagents

If human blood-derived components are contained in constituent reagents, submit test results that rule out the presence of HBV and HIV as well as the test results of HCV.

G. Manufacturing Method

Provide the following information in detail by referring to Appendix 3.

- (1) In principle, describe all processes from acceptance to release decision of (a) raw materials and intermediates of constituent reagents containing reactive ingredients and (b) constituent reagents not containing reactive ingredients. “Intermediates” in this context mean those containing reactive ingredients. The performance of finished products must be guaranteed by acceptance testing (purchase management) in the quality system for manufacturing the *in vitro* diagnostic product. If any of the constituent reagents are marketed as a single product for refilling, provide a statement to that effect.
- (2) Describe in a plain manner the manufacturing process and quality tests, along with the information on manufacturing sites involved in the process (name, and registration number if acquired), by using flowcharts, etc. If the manufacturing process takes place at several manufacturing sites (including the case where a product is manufactured at several manufacturing facilities at a single manufacturing site), the relationship between the sites (or facilities) must be described.
- (3) Provide the purpose and overview of each quality test and describe the relationship between each test and the product specifications.
- (4) If a proposed product incorporates another *in vitro* diagnostic product that has been approved or certified or submitted for marketing notification, the applicant must provide the name of the MAH of the incorporated product, its principal place of business and MAH license number, and the approval/certification/notification number of the incorporated product.
- (5) If a drug substance of the *in vitro* diagnostic product has been registered in a drug master file, provide the following information in the section of the manufacturing site of the drug substance: the name and address of the MAH, the name and address of the manufacturing site, and the registration number and date of the drug master file. If the manufacturing site is required to obtain a drug manufacturing license, state the license category, license number, and license date. If the manufacturing site is required to obtain an *in vitro* diagnostic manufacturing registration, state the registration number and registration date. If the manufacturing site is currently applying for a

manufacturing license (certification) or registration, provide a statement to that effect.

H. Clinical Performance Data

- “Clinical Performance Data” mean results from clinical studies of *in vitro* diagnostics not used directly in the human body.
- The data should include, in principle, results of at least 150 specimens (including specimens within normal ranges) at two or more facilities. A specimen number less than 150 may be acceptable if the number guarantees statistical analyses and adequate clinical evaluation.
- Create the data giving due consideration to the target disease or pathology, sensitivity and specificity in relation to the disease, abnormal specimens (hemolysis, chyle, jaundice, etc.), and the effects of drug administration.
- In principle, applicants are allowed to use the results of clinical performance studies conducted outside Japan. However, applicants should decide whether to use results of studies conducted outside Japan, based on the effects of ethnic differences between Japanese and non-Japanese populations, differences in environmental factors and clinical practice between Japan and foreign countries, etc. on the performance and clinical significance of the proposed *in vitro* diagnostic product.
- In principle, Clinical Performance Data are not required unless the application is for a novel product. This shall not apply, however, if new clinical significance arises.

6. Others

Standards of Blood Typing Antibodies (draft)

If the application is for a blood typing product that necessitates a revision to the “Standards of Blood Typing Antibodies,” submit the revised version (draft) of the standards for reference.

Chapter IV Post-approval Changes Requiring Partial Change Approval Application or

Minor Change Notification

The basic principles are provided below. See Appendix 4 for specific cases.

(1) Post-approval changes requiring application for new product approval

An application for new product approval must be submitted if an approved *in vitro* diagnostic product undergoes a post-approval change in reactive ingredients, quantity, and intended use, etc. that does not fall within the scope of minor changes.

(2) Post-approval changes requiring partial change approval application

A partial change approval application must be submitted, in principle, if an approved *in vitro* diagnostic product undergoes a post-approval change that does not impair the nature of the product. Due consideration should be given to the following points.

- (i) The partial change approval application form must be accompanied by a copy of the Marketing Approval Document of the product.
- (ii) The “Remarks” column of the application form must provide a table comparing pre- and post-changes with detailed reasons for the change. Further, describe the history of the previous approval(s).
- (iii) If a partial change approval application is submitted only to extend the approved shelf life, it will be handled expeditiously. Write “*cho*” in Chinese character in red ink on the application form. Submit data on setting of the shelf life with the application form.

(3) Changes requiring minor change notification

Even if an approved *in vitro* diagnostic product undergoes a post-approval change, a partial change approval application is not required as long as the change is minor and does not affect the performance of the product. Instead, a minor change notification must be submitted within 30 days of the change. The minor change notification form must be accompanied by a copy of the Marketing Approval Document of the product.

(4) Changes not requiring partial change approval application or minor change notification

Even if an approved *in vitro* diagnostic product undergoes a post-approval change, neither a partial change approval application nor minor change notification is required as long as the change is extremely minor and does not affect the

performance of the product. Other changes not relevant to the approved product information do not require a minor change notification.

(5) Minor change notification under partial change approval application

A minor change notification can be submitted during the review period of a previously submitted partial change approval application of the same product. However, if the changes proposed by both the notification and application are described in the same section of the notification (application) form, the partial change approval application must be replaced by a new one that contains all information regarding the changes proposed by the notification.

Chapter V Transitional Measures

Applications for marketing approval shall be handled as follows:

- (1) Handling of the application form for marketing approval and the submission data
 - 1) If the product has been submitted for marketing approval before enforcement of the Act,* its regulatory review is conducted based on the application form and submission data that were prepared and submitted in accordance with the former Act.†

There may be cases where a product is submitted for approval before enforcement of the Act* but the registration of its manufacturing site(s) expires after enforcement of the Act.* If the manufacturing site is subject to registration under the Act,* its registration must be renewed before approval. If the manufacturing site is not subject to registration under the Act,* its registration need not be renewed before approval.
 - 2) If the product is submitted for marketing approval after enforcement of the Act,* its regulatory review is conducted based on the application form and submission data that were prepared and submitted in accordance with the Act.* However, submission data prepared in accordance with the former Act† are also accepted as long as the application is submitted on or before March 31, 2015.
- (2) Handling of data on conformity to the standards stipulated in Article 41, Paragraph 3 of the Act*
 - 1) If the product has been submitted for approval before enforcement of the Act,* data on conformity to Essential Standards that have already been prepared and submitted in accordance with the former Act,† can be substituted with data prepared in accordance with the “Handling of Data Attached to Marketing Approval Document for *In Vitro* Diagnostics” (PFSB/ELD/OMDE Notification No. 0331005, dated March 31, 2008 by the Director of the Office of Medical Device Evaluation, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW; hereinafter referred to as the Equivalence Notification).
 - 2) Chapter III clarifies the details of data that should be submitted with the application form for marketing approval. Among these submission data, those

falling under “D. Conformity to the Standards Stipulated in Article 41, Paragraph 3 of the Act” can be substituted with data prepared in accordance with the Equivalence Notification during, only if the product is submitted for marketing approval on or before November 24, 2015.

- 3) Essential Standards applies to products submitted for marketing approval on or after November 25, 2015. Submit data prepared in accordance with Essential Standards for applications if the product filed on or after the data. The Equivalence Notification will be abolished as of November 24, 2015.

* The Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics

† The Pharmaceutical Affairs Act.

Appendix 1

Examples of Descriptions of Manufacturing Method

1. The kit contains the following:

[1] Enzyme preparation Manufactured by ○○○, △△△, and others.

[2] Diluent for enzyme preparation Manufactured by ××× and others.

[3] Coloring solution Manufactured by ◇◇◇ and others.

The kit is a combination of the above constituent reagents [1], [2], and [3]. Each reagent may be manufactured separately as a product for refilling.

2. Name of manufacturing sites and the manufacturing process

Name of manufacturing site	Manufacturing process
Manufacturing site A	Designing
Manufacturing site B	Filling
Manufacturing site C	Storage

* Explain the relationship between each manufacturing process.

Appendix 2

Examples of Descriptions of Manufacturing Sites of Products Proposed for Marketing

Example 1 If each manufacturing process takes place at a different manufacturing site

Name of manufacturing site	Registration number	Manufacturing process
○○○ Plant	...	Designing
△△△ Plant	...	Filling
☆☆☆ Plant	...	Storage

Example 2 If several manufacturing processes take place at a single manufacturing site

Name of manufacturing site	Registration number	Manufacturing process
○○○ Plant	...	Designing
□□□ Plant	...	Filling, storage

Example 3 If final container filling takes place at two registered manufacturing sites

Name of manufacturing site	Registration number	Manufacturing process
○○○ Plant	...	Designing
△△△ Plant	...	Filling
▲▲▲ Plant	...	Filling
☆☆☆ Plant	...	Storage

Example 4 If the facility where designing takes place has the same location as the main office of the marketing authorization holder

Name of manufacturing site	Registration number	Manufacturing process
××× Co., Ltd.	88AAA88888	Designing
□□□ Plant	...	Filling
☆☆☆ Plant	...	Storage

* If the name of a marketing authorization holder (e.g., ××× Co., Ltd.) is entered in the “Name of manufacturing site” column, “88AAA88888” should be entered in the “Registration number” column.

Appendix 3

Examples of Descriptions of Manufacturing Method

1. The kit contains the following:

[1] Enzyme preparation Manufactured by ○○○, △△△, and □□.

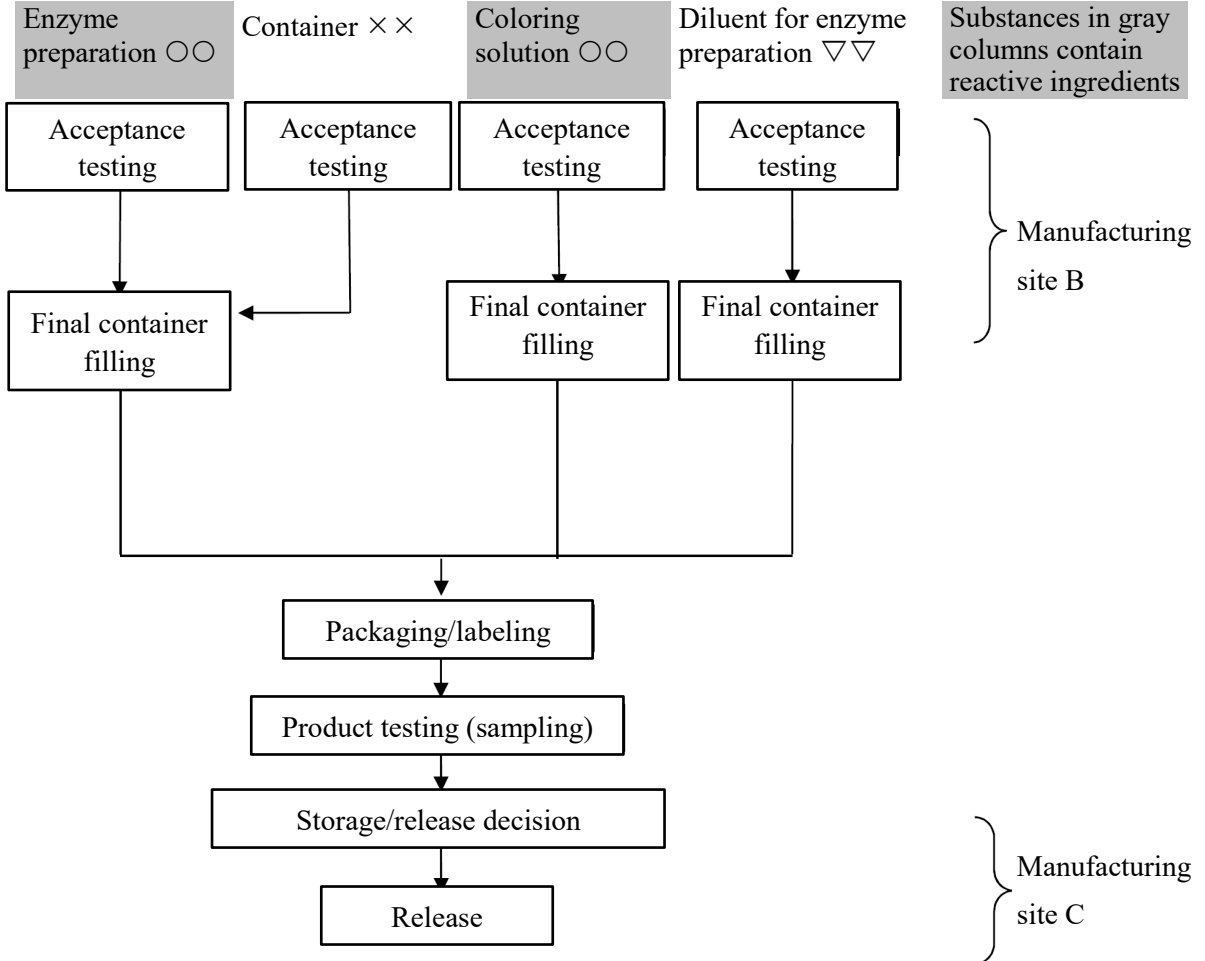
[2] Diluent for enzyme preparation Manufactured by ××× and ▽▽▽.

[3] Coloring solution Manufactured by ◇◇◇ and ■■■.

The kit is a combination of the above constituent reagents [1], [2], and [3]. Each reagent may be manufactured separately as a product for refilling.

2. Manufacturing Process Flow

Manufacturing Site for Designing: Manufacturing site A



Note: The process flow chart should include a description about a container only if its shape or structure affects the performance.

3. Name of manufacturing site, registration number, and manufacturing process

Name of manufacturing site	Registration number	Manufacturing process
Manufacturing site A	×××	Designing
Manufacturing site B	○○○	Filling
Manufacturing site C	△△△	Storage

4. Quality Tests

Quality tests (may be provided in a separate table.)

- Quality tests for acceptance testing of the enzyme preparation: Determination of potency, visual inspection (color tone), etc.

(Explain the relationship with test attributes listed in the “Product specifications” column.)

- Quality tests for acceptance testing of the coloring solution: Visual inspection (color tone), pH of the coloring solution, etc.

(Explain the relationship with test attributes listed in the “Product specifications” column.)

(The rest is omitted.)

Appendix 4

Scope of Partial Change Approval Application and Minor Change Notification for *In Vitro* Diagnostics

1. Name

(1) Generic name

Minor change notification must be submitted if the generic name or brand name (series name) of a product series is changed. This applies to all constituent products, except for those belonging to categories that require partial change approval application.

Example (in the case of a product series [generic name, Class III Series for Immunoassay] consisting of an approved reagent [Class III] and a certified reagent [Class II] for immunoassay):

Minor change notification must be submitted when the generic name (Class III Series for Immunoassay) is changed because of addition of a certified reagent for biochemical assay (Class II) to the product series. (Submit an application for partial change certification of the certified reagent for biochemical assay. After obtaining the certification, submit a minor change notification for the approved product series.)

(2) Brand name

- (a) Minor change notification must be submitted when the brand name is changed because of a change of the trademark.
- (b) Partial change approval application must be submitted when the brand name is changed unless the change falls under a minor change notification.

Example:

- When a brand name is changed in order to ensure uniformity in brand names to improve the corporate identity.
- When a brand name is changed to make it consistent with measurement item names that have been changed or added in response to advances in science.

2. Intended use

- (a) Minor change notification must be submitted when the abbreviation of a target analyte is changed when both the official name and its abbreviation are given.
- (b) Partial change approval application must be submitted when:
 - (i) a clinical significance is added.
 - (ii) a specimen type is added.
 - (iii) a qualitative test is added to a quantitative test.
 - (iv) a quantitative test is changed to a qualitative test.

Note: When a qualitative test is changed to a quantitative test, or a quantitative test is added to a qualitative test, the product must be submitted for marketing approval as a separate product.

3. Shape, Structure, and Principle

- (a) Minor change notification must be submitted when:
 - (i) the name of a constituent reagent is changed but the reagent itself remains unchanged.
 - (ii) the number of reagents (standard solution, control, etc.) is increased or decreased.
- (b) Partial change approval application must be submitted when:
 - (i) a change is made to the shape or structure that affects the performance.
 - (ii) the number of constituent reagents containing reactive ingredients is increased or decreased.

Note: When the measurement principle is changed, the product must be submitted for marketing approval as a separate product. When a change is made to the form or materials of non-reactive reagent(s) described in the Marketing Approval Document, the MAH is not required to submit a partial change approval application or a minor change notification as long as the change does not affect the performance.

4. Reactive Ingredients

- (a) Minor change notification must be submitted when only name of the ingredient is changed.
- (b) Partial change approval application must be submitted when:
 - (i) the actual amount is changed.
 - (ii) the animal species is changed.
 - (iii) the probe nucleotide sequences are changed but the binding site of the nucleic acid probe remains unchanged.

Note: When an *in vitro* diagnostic product using an antigen-antibody reaction undergoes a change in its primary antibodies from polyclonal to monoclonal antibodies, the product must be submitted for marketing approval as a separate product. Neither a partial change approval application nor minor change notification is required when the way of describing a quantity unit is changed after the unit becomes compendial.

5. Product Specifications

Partial change approval application must be submitted when:

- (i) performance testing is changed.
- (ii) the performance testing method is changed without a change in the acceptance criteria.
- (iii) the acceptance criteria for quality control testing (e.g., absorbance for sensitivity testing) are changed because of a change in the standard product or measurement instrument

Note: When a change is made to the measurement range (detection sensitivity) described in the Marketing Approval Document, the MAH is not required to submit a partial change approval application or a minor change notification.

6. Directions for Use

- (a) Minor change notification must be submitted when:
 - (i) the reagent preparation method is changed.
 - (ii) the name of the dedicated instrument is changed.

- (iii) the description of operating procedure is simplified without affecting the performance.

Example:

- When the description of the location of button(s) of the dedicated instrument is deleted.
 - When a change is made to the description of operation of general reagents (i.e., those not classified as constituent reagents of the kit).
 - When the description of usage is deleted (without affecting the reaction system).
- (iv) a change is made without affecting the method of quality control provided in the “Product Specifications” column (a change not requiring a partial change approval application).

Example:

- When the description of the amount of specimens or reagents is changed from specific values to a range within the approved scope (e.g., when the description of specimen amount is changed from “0.2 mL and 0.5 mL” to “0.2 to 0.5 mL”).
- When the description of the amount of specimens and reagents is changed from specific values to fluid volume ratio, without changing the approved ratio itself.
- When both manual and automatic analysis method are described but either of them is deleted.

(b) Partial change approval application must be submitted when:

- (i) a change is made to the specimen collection procedures or storage conditions.
- (ii) a change is made to the wavelength to be used.

Note: When a change is made to the form of the constituent reagent(s) described in the Marketing Approval Document, the MAH is not required to submit a partial change approval application or a minor change notification as long as the change does not affect the performance.

7. Manufacturing Method

(a) Minor change notification must be submitted when:

- (i) a change is made that falls within the scope of a minor change notification, as stipulated in 2. (2) of “Acceleration of Procedures for Change and Addition of Manufacturing Sites for Medical Devices and *In Vitro* Diagnostics” (PFSB/ELD/OMDE Notification No. 1119-7 and PFSB/CND Notification No. 1119-12, dated November 19, 2014, issued jointly by the Counsellor of Minister’s Secretariat [for Evaluation and Licensing of Medical Device/Cellular and Tissue-based Products] and the Director of the Compliance and Narcotics Division, Pharmaceutical and Food Safety Bureau, MHLW; hereinafter referred to as the Expedited Review Notification)
- (ii) the distribution of a single product (for refilling) is changed or added.
- (iii) the description of one or some of manufacturing sites involved in the process, is removed.

Example:

In a case where several manufacturing plants have been subcontracted to carry out the same process but one or some of them are removed from the subcontract, requiring the removal of the description of the plant(s).

Note: This change causes a discrepancy between the combination of manufacturing sites recorded on the compliance certificate and the actual combination of manufacturing sites. If a new compliance certificate that records the actual combination of manufacturing sites is not issued before the date of a periodic compliance inspection, the MAH must submit an application for a periodic compliance inspection that examines the actual combination of manufacturing sites.

(b) Partial change approval application must be submitted when a change is made that falls within the scope of partial change approval application, as stipulated in 2. (2) of the Expedited Review Notification

8. Storage Conditions and Shelf Life

Partial change approval application must be submitted when a change is made to the storage conditions or shelf life.

9. Manufacturing Sites of the Product to Be Marketed

(a) Minor change notification must be submitted when the description of a manufacturing site(s) is changed because of another change falling within the scope of the minor change notification, as stipulated in “7. Manufacturing Method”

(b) Partial change approval application must be submitted when the description of a manufacturing site(s) is changed because of another change falling within the scope of the partial change approval application, as stipulated in “7. Manufacturing Method”

Attached Form

Constituent Product Data Sheet

Name	Generic name	
	Name of constituent product	
Intended use		
Shape, structure, and principle		
Reactive ingredients		
Product specifications		
Directions for use		
Manufacturing method		
Storage conditions and shelf life		
Manufacturing sites of the product proposed for marketing	Name	Registration number
Remarks		

Note:

- 1 Use A4 format (JIS).
- 2 Create a Constituent Product Data Sheet for each constituent product.
- 3 If the constituent product has been approved or certified individually or its notification has already been submitted individually, provide the name of the product (generic and brand names), the approval/certification/notification number, the name of the marketing authorization holder, and the MAH license number in the “Remarks” column.