

**Provisional Translation (as of March 2010) \***

PFSB/ELD/OMDE (*Yakushokuki*) Notification No. 0216003

February 16, 2005

To: Directors of Health Departments (Bureaus)  
Prefectural Governments

From: Director of Office of Medical Devices Evaluation,  
Evaluation and Licensing Division,  
Pharmaceutical and Food Safety Bureau,  
Ministry of Health, Labour and Welfare

Re: Handbook for Preparation of Summary Technical Documentation Submitted in  
Applications for Marketing Approval for Medical Devices

According to the PMSB/ELD (*Iyakushin*) Notification No. 85 by the Director of Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau, Ministry of Health, Labour and Welfare (MHLW), dated January 28, 1999, "Handbook for Preparation of Summary of Data Submitted in Applications for Approval for New Medical Devices," MHLW has encouraged applicants to prepare a "summary of data (*Shiryō-gaiyō*)," which concisely summarizes the data for submission, when filing an application for approval to manufacture (import) a new medical device. In addition, MHLW has, on a trial basis, accepted the Summary Technical Documentation (STED) format, which has been developed by the Global Harmonization Task Force (GHTF), as a summary of data according to the PFSB/ELD (*Iyakushin*) Notification No. 0201099 by the Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, dated February 1, 2002, "Trial Acceptance of Summary Technical Documentation (STED) for Regulatory Review of Medical Devices."

Based on the above developments, MHLW has made the following decision concerning the review of applications for approval to market medical devices in accordance with the Pharmaceutical Affairs Law (Law No. 145 of 1969; hereinafter referred to as the "Law") as amended in the Law for Partial Revision of the Pharmaceutical Affairs Law and Blood

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\* 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.

Collection and Donation Services Control Law (Law No. 96 of 2002). MHLW will request applicants to prepare a summary of data according to the GHTF STED format and to submit it as the summary technical documentation (STED) in filing an application for marketing approval, excluding those for medical devices which are evaluated by confirming their conformity to the standards specified by MHLW beforehand per generic name. As a guideline for preparing the STED, MHLW has developed the Handbook for Preparation of Summary Technical Documentation Submitted in Applications for Marketing Approval for Medical Devices. You are requested to check the information below, and to notify relevant business parties and organizations under your jurisdiction of such information.

Please note that copies of this Notification will be sent to the Chief Executive of the Pharmaceuticals and Medical Devices Agency; the Chairperson of the Japan Federation of Medical Devices Associations; the Chairperson of Medical Devices and Diagnostics Subcommittee, the American Chamber of Commerce in Japan; and the Chairperson of Medical Devices Committee, European Business Council in Japan.

#### I. Basic Concepts of Summary Technical Documentation

The summary technical documentation (STED) should provide an overview of the medical device for which a marketing application is submitted by an applicant, and it must be prepared by the applicant based on the data submitted in the application. The STED accurately and concisely summarizes the course of development, including the applicant's views and basis for their judgment during the development process, and key points on quality, efficacy, and safety, by incorporating the applicant's evaluation of clinical benefit. The STED thus prepared serves as an extremely valuable resource for the reviewers who conduct the evaluation to grasp the overview of the medical device for which under review.

The STED, which has been newly adopted as a format for a summary of data, was developed by the Global Harmonization Task Force (GHTF). The STED appropriately summarizes the technical documents that are maintained by marketing authorization holders or manufacturers of medical devices to ensure the quality, efficacy, and safety of the medical devices they have manufactured or imported. The marketing authorization holders or manufacturers must maintain such technical documents, regardless of whether or not they file an application for marketing approval.

This handbook is intended to standardize the format and content of a STED to help an applicant streamline their preparation process of a STED while assisting reviewers who evaluate the

application understand the content of the STED, thereby expediting the regulatory review. At the same time, the STED contributes to the improvement of the review because comparison would be easier to make between similar medical devices.

This handbook is not designed for submission data for any particular medical device, but encompasses all data that should be submitted for the application for marketing approval. Therefore, when preparing a STED for a medical device, it is important to develop one that appropriately covers items in the scope needed for evaluating the medical device by referring to this handbook.

This Notification shall not apply to the applications for marketing approval for medical devices that require a preliminary evaluation concerning confirmation of the quality and safety of the product prior to clinical trials according to the Guidelines for Assurance of Quality and Safety of Drugs and Devices Processed from Cells and Tissues of Human Origin (PMSB [*Iyaku*] Notification No.1314 by the Director-General of Pharmaceutical and Medical Safety Bureau, dated December 26, 2000) and those for medical devices which are claimed to conform to the applicable approval standards.

## II. General Points to Consider

1. The form must be JIS A4 in size, and printed on both sides of papers, in principle.
2. The information must be organized in the sequence shown below, and the overall structure must be as shown in Annex 1.

While the Annex 1 encompasses most of the data in the Appendix Table 1 of the PFSB (*Yakushoku*) Notification No. 0216002 by the Director-General of Pharmaceutical and Food Safety Bureau, dated February 16, 2005, “Applications for Marketing Approval for Medical Devices,” the STED should include the scope of the data, which is to be submitted in a marketing application, corresponding to the features of the medical device for which approval is sought.

3. Use serial numbers for each page, and provide a table of contents for the entire STED.
4. Following the cover page, insert the form shown in Annex 2 to provide an overview of the product, and attach color photographs or clear color printed matters that can be used to confirm the external appearance and dimensions of the medical device. Next, provide a table of contents for the entire STED.
5. In principle, allocate one or two pages of “Summary” for each section of summaries of design verification and design validation, and provide a summary of the entire test in the section and the applicant’s view (1 or 2 pages). After the “Summary,” provide an outline of the test method and test results for each test in the section, and provide the necessary

discussion. In this case, use tables and figures, whenever possible.

6. To provide appropriate description, make sure to clearly distinguish the facts based on evaluation data from the applicant's views or interpretations. In addition, clearly distinguish the findings based on evaluation data from those based on reference data.
7. Clarify the relationship between the contents of STED and the corresponding data for submission to allow the reviewers to promptly and accurately find the relevant section in the STED.

To this end, it is recommended that the applicant print the data number in an upper corner of each page. If the data for submission consists of many pages, it is desirable that a page index be provided by the applicant.

8. Avoid redundant information to the possible extent, and clarify the sections where the desired information can be found.
9. If an approval standard, or guideline, etc. established by MHLW is available for the product, clarify whether the test was conducted according to the standard or guideline. If the test deviates from the standard or guideline, state the sections, the reason and justification for the deviation. The same procedures will apply to standards such as those of Japan Industrial Standards (JIS), International Organization for Standardization (ISO), and International Electrotechnical Commission (IEC).
10. Provide a list of abbreviations on the reverse side of the cover page of the STED.
11. In addition to the above, take the following points into account.
  - (1) Use headings and subheadings whenever possible, and provide itemized descriptions if possible. Also, use heading and subheading symbol and number schemes that facilitate clarity.
  - (2) Use font size that is easy to read (e.g., 12 points), and use fonts such as Gothic where emphasis is necessary.
  - (3) Insert a line break or page break, where appropriate.
  - (4) Use foldout pages only when necessary.
  - (5) Always clarify units of numerical values such as measurements.
  - (6) Use the appropriate academic terminology. Special attention should be paid in the case of translation. It is desirable to have the translation proofread by an expert.
  - (7) Use titles for figures and tables that clearly represent the contents.
  - (8) When quoting figures and tables directly from their source documents, note the data number and page number of the source.
  - (9) When modifying figures or tables instead of using them directly from the source, make a note to that effect.
  - (10) When quoting another section of the STED, clarify the section being quoted.
  - (11) When quoting other publications, provide a bibliography of the publications at the

bottom of the page or at the end of each section.

- (12) When showing the results of statistical analysis, clarify the analytical method, and show such basic statistical values as the sample size, mean, and standard deviation; test statistics; and such test results as  $p$  value. In addition, also show the point estimate and interval estimate, as necessary. Illustrate analytic results, whenever possible.
- (13) If a statistical test has been conducted, show the test method. If the test results are significant, use appropriate symbols to indicate the significance level. If the results are complicated, add an explanation or otherwise to facilitate understanding.
- (14) Provide the initial value, as necessary.

[Attachment]

Handbook for Preparation of Summary Technical Documentation Submitted in Applications for  
Marketing Approval for Medical Devices

1. Overview of Product

1.1 Summary of Product

Use the form shown in Annex 2 to provide a summary of the product, and attach color photographs or clear color printed matters that can be used to confirm the external appearance and dimensions of the medical device.

1.2 Origin or History of Discovery and History of Development

(1) Explain as follows: When, where, by whom the relevant product was developed based on what idea, and what triggered the development. Then, for what purpose the product was developed, how it was investigated, and what was developed as a result. Eventually, what data were used to fully confirm efficacy and safety and how useful the product is.

(2) Explain concisely how the consideration was advanced in each process (determining the design requirements, preparing documents on design results, evaluating design results, verifying the design, validating the design, and changing the design in the development process).

In this section, explain all the items that are required to evaluate the quality, durability, reliability, safety, indications, performance, and benefit of use of the medical device developed.

In addition, if there is a problem found in the development process or a change made to the development plan, then explain the nature of and reason for the problem or change, and the justification for the action taken.

(3) State when non-clinical studies and clinical studies were started and the rationale for the decision of advancement from non-clinical studies to clinical studies. If the studies were advanced differently from those for similar medical devices, then explain the differences and the justification for the approach taken.

(4) If there is a problem found in the development process or a change made to the development plan, then explain the nature of and reason for the problem or change, and the justification for the action taken (e.g., if the intended use, target patients, or product specifications are considerably different from those in a country where the medical device has been introduced).

- (5) Provide a figure that shows the course of development, including the beginning and ending dates (month/day/year) of each study in a chronological format for design verification and design validation.
- (6) If the medical device has been created in a joint development, prepare a work allocation chart (participating or involved companies, application type, and allocation of work). Work allocation may be incorporated in the figure that shows the course of development in above (5).
- (7) If the applicant has developed a medical device whose structure and principle are the same as those of the medical device for which approval is being sought, but whose model, energy output, applicable body part, or intended use is different from those of the medical device, then provide an outline thereof.

### 1.3 Usage Conditions in Foreign Countries

- (1) Show the license and usage conditions in foreign countries, including the number of countries in which the medical device is licensed and used, names of major countries in which the medical device is licensed and used, brand names (in original languages), month and year of obtaining license, month and year of starting use, approximate number of usage per year, intended use, indications, and usage method. Provide the latest possible information by country in a list. Also, provide such information in a similar manner even in the case where application for license is pending approval.
- (2) As for malfunctions that have previously been reported in the use in foreign countries, provide an outline of the types and frequency of malfunctions in a list format.
- (3) If the medical device is imported into Japan from a foreign country where it is not used, explain the reason.
- (4) Describe the year and month of the survey.
- (5) Promptly report any change in the information provided under above (1) through (3) after the STED has been prepared. In particular, if a decision is made on whether or not a license is granted in major countries where the application was pending approval or when there is a change in the incidence of serious malfunctions with a relatively high probability of directly endangering the patient's life, promptly report in writing to the Office of Review Administration of the Pharmaceuticals and Medical Devices Agency. Other malfunctions should be updated whenever the STED is revised.
- (6) When filing a partial change application for the approved information on a product for which a marketing approval has already been granted, also state the usage conditions in Japan and occurrence of malfunctions in Japan.

## 2. Essential Principles and Conformity to the Essential Principles

## 2.1 List of Referenced Standards

- (1) List the standards that are used to demonstrate conformity to the medical device standards set forth by the Minister of Health, Labour and Welfare according to Article 41, Paragraph 3 of the Law (hereinafter referred to as the "Essential Principles") along with the sources, years, and standard numbers.

## 2.2 Essential Principles and Evidence of Conformity

- (1) Explain the conformity to each requirement of the Essential Principles. The test records or test results that are used to explain conformity to the Essential Principles are provided under the section 4. Summary of Design Verification and Validation Documents, the section 6. Risk Analysis, and the section 7. Manufacturing Information. Indicate where the test records or test results are provided for each requirement of the Essential Principles.

In addition, justify the validity of standards or criteria that were used to explain conformity to the Essential Principles, and the conformity of the medical device to such standards or criteria. If there are no other standards, criteria, etc., which serve as reference, explain the method of tests that were conducted to prove conformity to the Essential Principles, and explain that the test results can be used to prove conformity to the Essential Principles.

## 3. Device Description

### 3.1 General Information

- (1) Describe the intended use of the device. It should be consistent with the description of "Intended Use, Indications" in the appendix of the application form.
- (2) Describe the indicated patients and diseases, subject inclusion criteria, and contraindications and prohibitions in accordance with the descriptions of contraindications, etc. on the draft instructions for use.
- (3) Copy the illustration of the device and the description for the features of functions of each part from the Appendix (Shape, Structure, and Principle) of the application form.
- (4) In the case of medical electrical equipment, copy the description for the principle of the device, including the principle of controls, from the Appendix (Shape, Structure, and Principle) of the application form.
- (5) Describe the operation method of the device based on the "Operation or Usage Method" column on the application form.
- (6) Explain that the device for which approval is sought corresponds to the generic name provided in the "Name" column on the application form.



### 3.2 Raw Materials

Copy the information in the “Raw Materials or Components” column on the application form.

### 3.3 Product Specifications

- (1) State the specifications of the device provided in the “Product Specifications” column on the application form.
- (2) Explain that the established product specifications are necessary and sufficient to ensure the efficacy, safety, and quality of the product for which approval is sought, based on the Essential Principles and other referenced standards. When adopting appropriate standards, whether domestic or overseas, provide the scientific justification for adopting such standards.

Also, state the rationale for the judgment that the established test items are necessary and sufficient based on the current levels of scientific and technical knowledge.

- (3) When the applicant chooses not to establish test items that must normally be set up for a similar medical device, state the reason and the rationale for the decision.

### 3.4 Storage Method and Expiration Period

- (1) When the storage method and expiration period are stated on the application form, explain the appropriateness of the storage method and expiration period based on the information provided in the “Storage and Expiration Period” column.

### 3.5 Comparison with Similar Medical Devices

- (1) State the efficacy, safety, product features, etc., focusing on differences revealed through comparisons with similar medical devices already on the market in terms of structure, principle, and clinical use. Also, fill in the column taking the medical usefulness of the medical device into account.
- (2) When comparing the medical device with similar medical devices already on the market, select those that are similar in terms of intended use, product specifications, usage method, etc. Using the latest instructions for use, whenever possible, prepare a list of generic name, brand name, date of approval, intended use, and indications, and, as necessary, structure and principle, raw materials, product specifications, and usage or operation method. Select the appropriate items for comparison according to the properties of the medical device. In particular, pay special attention to the selection of items for comparing structure and principle, raw materials, and product specifications. Also, state the sources of data for the medical device used for the comparison.
- (3) Follow the rules below when preparing the list as stipulated in (2) above.

- 1) When there is more than one similar medical device, list them in reverse-chronological order starting with the most recently approved, licensed, or notified medical device.
- 2) State the re-examination and re-evaluation dates (month/day/year) for medical devices for which re-examination and re-evaluation have been completed.
- 3) If a comparative clinical trial (including blind studies) using a comparator has been conducted, in principle, enter in the list the medical device used as a comparator following the medical device for which approval is sought, and in the “Note” column, state the type of comparative clinical trial and make a note to the effect that the medical device was used as a comparator in the study.

#### 4. Summary of Design Verification and Validation Documents

##### 4.1 General Information

###### 4.1.1 Declaration of Conformity to Standards

Declare that the relevant product is manufactured to conform to the Essential Principles and the Quality Management System for Medical Devices and *In Vitro* Diagnostics. The declaration of conformity must separately be attached to the application form. The applicant is advised to prepare the declaration of conformity according to ISO 17050-1 “Conformity Assessment - Supplier’s Declaration of Conformity - Part 1: General Requirement.”

##### 4.2 Summary of Design Validation

Prove conformity to the standards used in the explanation to demonstrate conformity to Essential Principles (e.g., JIS T 0993-1 “Biological Evaluation of Medical Devices - Part 1: Evaluation and Testing,” JIS T 0601-1 “Medical Electrical Equipment - Part 1: General Requirements for Safety,” and standards concerning radiation safety and other safety-related issues), and describe tests listed as the basis for conformity to the Essential Principles (excluding clinical trials). Refer to the major points to consider that are provided in sections 4.2.1 and thereafter.

If the product’s conformity to the above standards has been certified by a certification body which is accredited as conforming to ISO 17025: “General Requirements for the Competence of Calibration and Testing Laboratories” (published by the International Organization for Standardization) by an IAF member accreditation body, or by a certification body registered according to Article 57, Paragraph 1 of the Industrial Standardization Law (Law No. 185 of 1949) (hereinafter referred to as “JNLA” registration), a description to that effect is acceptable.

Even if a medical device conforms to the standards, clinical trial results or performance tests

are required if the applicant claims that the device has a new efficacy etc.

#### 4.2.1 Tests to Support Safety

(1) For “Summary,” provide a list of the test items, test methods, test results, testing laboratory, data number, etc. of tests to support safety, and also provide an outline for each test.

Also, state the rationale for the judgment that the test items performed are necessary and sufficient to evaluate safety based on the current levels of scientific and technical knowledge.

(2) In “Summary,” also discuss the relationship between the results of the tests to support safety and the product specifications proposed in the application.

In addition, state the clinical positioning and features of the medical device in comparison with similar medical devices, as necessary.

(3) Provide a list of the test methods and test results for each test, summarize the findings, and add necessary discussions. Refer to major points to consider in sections 4.2.1.1 and thereafter.

(4) Use figures and tables to describe the test results, whenever possible.

#### 4.2.1.1 Physical and Chemical Properties

For “Summary,” describe the selected test items and an outline of test results for physical and chemical properties. If the medical device uses dental materials or polymer materials, refer to the information below in selecting appropriate items by taking the features of the medical device fully into account.

As the properties of components may affect the identity of the medical device, state the chemical structure, infrared absorption, ultraviolet absorption, atomic absorption, melting point, boiling point, durability, hardness, color tone, leachables, surface properties, etc. according to the properties of the material.

When selecting the items for the physical and chemical properties of dental materials, refer to the “Basic Principles for Biological Studies of Dental Materials” and “Basic Principles for Physical and Chemical Studies of Dental Materials” notified separately.

#### 4.2.1.2 Electrical Safety and Electromagnetic Compatibility

(1) For “Summary,” provide a concise list of the test items, test methods, testing conditions, reference values, test results, testing laboratory, data number, etc. of electrical safety and electromagnetic compatibility tests conducted, and also provide an outline for each

test.

In addition, state the rationale for the judgment that the test items performed are necessary and sufficient to evaluate electric safety and electromagnetic compatibility based on the current levels of scientific and technical knowledge.

- (2) When the applicant chooses not to conduct tests that must normally be done for a similar medical device, state the reason in the “Summary.”
- (3) Provide a list of the test methods and test results for each test, summarize the findings, and add necessary discussions.
- (4) Pay attention to the following points when describing tests:
  - 1) If an additional test is conducted during the development process, state the reason for and background to the decision.
  - 2) If a test does not meet the test method stipulated in JIS T 0601-1 “Medical Electrical Equipment - Part 1: General Requirements for Safety” or, for tests concerning electromagnetic compatibility, JIS T 0601-1-2 “Medical Electrical Equipment - Part 1: General Requirements for Safety - Section 2: Electromagnetic Compatibility - Requirements and Tests,” state the section where the test does not meet the requirements, the reason for the discrepancy, and the validity of the test.

4.2.1.3 Biological Safety
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- (1) For “Summary,” provide a concise list of test items, test methods, test results (e.g., positive, negative, IC50 value, histopathological examination results), testing laboratory, and data number for the biological safety tests conducted, and also provide an outline for each test.

Also, state the rationale for the judgment that the test items performed are necessary and sufficient to evaluate biological safety based on the current levels of scientific and technical knowledge.
- (2) When the applicant chooses not to conduct tests that must normally be done for a similar medical device, state the reason in the “Summary.”
- (3) Provide a list of test methods and test results for each test, summarize the findings, and add necessary discussions.
- (4) Pay attention to the following points when describing tests:

- 1) Provide the necessary findings and evaluation for each test.
- 2) Discuss the justification for an animal experiment model in connection with clinical use in human.
- 3) If an additional test is conducted during the development process, state the reason for and background to the decision.
- 4) If a test does not meet the test method stipulated in the PMSB/ELD (*Iyakushin*) Notification No. 0213001 by the Director of Evaluation and Licensing Division, dated February 13, 2003, “Basic Principles of Biological Safety Evaluation Required for Application for Approval for Manufacture (Import) of Medical Devices” and “Basic Principles for Biological Tests for Dental Materials” notified separately, state the section where the test does not meet the requirements, the reason for the discrepancy, and the rationale for the test.

4.2.1.4 Radiation Safety
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- (1) For “Summary,” provide a concise list of test items, test methods, testing conditions, reference values, test results, testing facility, and data number for the radiation safety tests conducted, and also provide an outline for each test.  
Also, state the rationale for the judgment that the test items performed are necessary and sufficient to evaluate radiation safety based on the current levels of scientific and technical knowledge.
- (2) When the applicant chooses not to conduct tests that must normally be done for a similar medical device, state the reason in “Summary.”
- (3) Provide a list of test methods (sample, measurement method, tolerance, or allowable deviation) and test results for each test, summarize the findings, and add necessary discussions.
- (4) Pay attention to the following points when describing tests:
  - 1) Describe compliance to laws concerning medical devices such as Chapter 4, Section 2 of the Enforcement Regulations of the Medical Service Law (Ministry of Health and Welfare Ordinance No. 50 of 1948).
  - 2) If an additional test is conducted during the development process, state the reason for and background to the decision.
  - 3) If a test does not meet the standards that are applicable to the individual medical device, state the section where the test does not meet the requirements, the reason for the discrepancy, and the validity of the test.

#### 4.2.1.5 Mechanical Safety

- (1) For “Summary,” provide a concise list of test items, test methods, testing conditions, reference values, test results, testing laboratory, and data number for the mechanical safety tests conducted, and also provide an outline for each test.  
Also, state the rationale for the judgment that the test items performed are necessary and sufficient to evaluate mechanical safety based on the current levels of scientific and technical knowledge.
- (2) When the applicant chooses not to conduct tests that must normally be done for a similar medical device, state the reason in “Summary.”
- (3) Provide a list of test methods (sample, measurement method, tolerance, or allowable deviation) and test results for each test, summarize the findings, and add necessary discussions.
- (4) Pay attention to the following points when describing tests:
  - 1) If an additional test is conducted during the development process, state the reason for and background to the decision.
  - 2) As to medical electrical equipment, if a test does not meet the test method stipulated in JIST 0601-1 “Medical Electrical Equipment - Part 1: General Requirements for Safety,” state the section where the test does not meet the requirements, the reason for the discrepancy, and the justification for the test.

#### 4.2.1.6 Stability and Durability

- (1) For “Summary,” provide an outline of test results on stability or durability (if the medical device has been sterilized by radio-sterilization, then information on material degradation due to sterilization is included), storage method, and discussions including whether an expiration date needs to be set.  
Also, state the rationale for the judgment that the test items performed are necessary and sufficient to evaluate stability and durability based on the current levels of scientific and technical knowledge.
- (2) Provide a list of testing conditions, measured items, and storage period for each test (e.g., long-term testing, accelerated testing, stress testing), summarize the test methods and test results, and add necessary discussions.

- (3) Explain the rationale for selection of the test methods.
- (4) If the application is submitted during a long-term stability testing, make a note to that effect.
- (5) If the medical device is intended to be used after re-sterilization, then describe the effect of the sterilization.

#### 4.2.2 Tests to Support Performance

- (1) For “Summary,” provide a list of test items, test method, test results, testing laboratory, and data number for the tests to support performance, and also provide an outline for each test.  
Also, state the rationale for the judgment that the test items performed are necessary and sufficient to evaluate performance based on the current levels of scientific and technical knowledge.
- (2) In addition, state in “Summary” the relationship between the results of the tests to support performance and the product specifications proposed in the application. Also, state the clinical positioning and features of the medical device in a comparison with similar medical devices, as necessary.
- (3) Provide a list of test methods and test results for each test, summarize the findings, and add necessary discussions.
- (4) Use figures and tables to explain test results, whenever possible.

#### 4.2.3 Tests to Support Efficacy

- (1) For “Summary,” provide a list of test items, test methods, usage method (or dosage and administration[CH1]), duration of use, control device, test results, testing laboratory, and data number for the tests to support efficacy and tests on mechanism of action, and also provide an outline for each test.  
Also, state the rationale for the judgment that the test items performed are necessary and sufficient to evaluate efficacy based on the current levels of scientific and technical knowledge.
- (2) Also, in “Summary,” state the course of investigating the mechanism of action, as well as the relationship of the results of the tests to support efficacy and the tests on

mechanism of action to the indications proposed in the application.

In addition, state the clinical positioning and features of the medical device in a comparison with similar medical devices, as necessary.

The information is not required, however, if the medical device has the same efficacy as that of the existing medical devices.

- (3) Provide a list of test methods and test results for each test, summarize the findings, and add necessary discussions.
- (4) Use figures and tables to explain test results, whenever possible.

4.2.4 Tests to Support Usage Method
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- (1) For “Summary,” provide a list of test items, test methods, usage method (or dosage and administration), test results, testing laboratory, and data number for the tests to support the usage method, and also provide an outline for each test, as well as the basis for establishing the usage method, volume used, etc.

Also, state the rationale of the judgment that the test items performed are necessary and sufficient to evaluate the usage method based on the current levels of scientific and technical knowledge. If necessary, provide a view on the relationship between the usage method and malfunctions in the medical device. The information is not necessary, however, if the usage method of the medical device is the same as that of the existing medical devices.

- (2) Provide a list of test methods and test results for each test, summarize the findings, and add necessary discussions.
- (3) Use figures and tables to explain test results, whenever possible.

4.3 Clinical Evidence
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- (1) For “Summary,” provide a list of study types (e.g., comparative clinical or open clinical trials), target patients, sample size, usage method (or dosage and administration), examination and observation items, duration of use, clinical trial period, name of representative study site, and data number for the clinical trial, and also provide an outline for each study.

- (2) When the applicant chooses not to conduct studies that must normally be done for a similar medical device, state the reason and the rationale for the applicant’s judgment



that the conducted clinical trials are enough to ensure that the quality, efficacy, and safety of the medical device would be evaluated appropriately.

#### 4.3.1 Clinical Trial Results

- (1) For each study, prepare a list of the study method (e.g., study objectives, study type, subject inclusion criteria, exclusion criteria, sample size, usage method, duration of use, observation period, combined therapy, examination and observation items and phase, evaluation method and evaluation criteria, principle investigator, name of representative study site and the number of study sites, and study period) and an outline of study results, provide the rationale for establishing the subject inclusion criteria, exclusion criteria, and usage method (or dosage and administration), breakdown of cases (e.g., number of patients included in the safety evaluation and number of patients included in the efficacy evaluation), reasons and breakdowns of cases in which the treatment was discontinued and of subjects who withdrew from the study or deviated from protocols, background information on patients (e.g., gender, age, in-patient or out-patient, primary disease, severity before use of the device, duration of disease, complications, duration of use, volume used), stratified analysis (as necessary), study results (describe results concerning efficacy and safety in detail), and conclusions. Use as much tables as possible when describing the above information.

For malfunctions, prepare a list of incidence by test and malfunction type, a list of incidence by background factor and malfunction type, a list of malfunctions (cases) (including details of symptoms, course of events, and comments by an attending physician), and summarize the occurrence of malfunctions, actions taken, and course of events. As to laboratory test results, prepare a list of abnormal changes in laboratory test values by test item, a list of cases with abnormal changes in laboratory test values, and an appropriate diagram of laboratory test values that shows the changes, and summarize them. If a serious malfunction or death has occurred, prepare a table of cases including the course of events, and discuss the relationship between those cases and the investigational device, taking the physician's judgment into account.

- (2) If a comparative study has been conducted, also state the reason for selecting the comparator when completing the description for above (1).
- (3) Attach a list of cases.

#### 4.3.2 Conclusion of Clinical Trial Results

- (1) Conclusion of efficacy

Prepare a list of efficacy by study and by background factor, and provide a conclusion.

(2) Conclusion of safety

Summarize the study results relating to safety provided in the section “4.3.1 Clinical Trial Results,” and provide a conclusion.

4.3.3 Miscellaneous
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Provide a summary of foreign clinical trial results for reference, as necessary.

5. Labeling
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5.1 Instructions for Use (Draft)
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(1) Provide the instructions for use (draft) and the data providing the basis for establishing them.

(2) Medical devices are classified as shown in the attachment to the Notification by the Director-General of Pharmaceutical and Food Safety Bureau, dated July 20, 2004, “Implementation of Specially Controlled Medical Devices, Controlled Medical Devices and General Medical Devices Specified by the Minister of Health, Labour and Welfare According to the Provisions of Article 2, Paragraphs 5 to 7 of the Pharmaceutical Affairs Law (Ministerial Notification) and the Specially Designated Maintenance and Management Required Medical Devices Specified by the Minister of Health, Labour and Welfare According to the Provisions of Article 2, Paragraph 8 of the Pharmaceutical Affairs Law (Ministerial Notification)” (hereinafter referred to as “Classification Notification”). If a medical device belongs to Class IV, or if it is a Class III medical device which is implanted or placed into the human body and of which malfunction is relatively likely to endanger the patient’s life, then make quotations from the instructions for use, in particular, adopted in major countries and compare those instructions for use with the Japanese one. Also, add the applicant’s discussion.

(3) If precautions are added to the instructions for use as a result of a risk analysis, state that the addition has been made to take measures against the risk.

(4) Enclose in a box the “Intended Use, Indications” in the instructions for use (draft), and describe the rationale for the intended use of the device, indications based on the test results that support the efficacy, test results that support the performance, and conclusion of clinical trial results.

- (5) Enclose in a box the “Operation or Usage Method” in the instructions for use (draft), and describe the rationale for establishing the operation or usage method based on the test results that support the usage method, test results that support the performance, and conclusion of clinical trial results.
  
- (6) Enclose in a box the WARNING and CONTRAINDICATIONS and PRECAUTIONS in the instructions for use (draft). For each item in the instructions for use, state the rationale for establishing the information based on non-clinical study and clinical trial results. If the medical device belongs to Class IV, or if it is a Class III medical device which is implanted or placed into the human body and whose malfunction is relatively likely to endanger the patient’s life, then explain the basis for establishing the information, referring to precautions adopted in major countries in which the medical device is used.

## 5.2 Label (Draft)

Provide the label information (draft) that must be affixed to the medical device according to the provisions of Article 63 of the Law.

Clearly distinguish the information that is placed directly on the medical device from the information that is placed on the primary package and secondary package, as necessary.

## 6. Risk Analysis

- (1) Refer to JIS T 14971 “Medical Devices - Application of Risk Management to Medical Devices” to perform risk analysis for the medical device, and submit the resulting information on the company structure and overview of implementation status of risk management. For the information below, explain that the foreseeable risk relative to the clinical benefits is acceptable.
  - a. Submit the data that summarize in a tabular format the risk analysis and risk mitigation measures for hazards (that are related to similar medical devices and include those having an association with the medical device for which approval is sought) against which the applicant is requested by MHLW, etc. to take safety measures.
  - b. If, as a result of risk management based on JIS T 14971, a serious hazard other than those described in above “a” is found, submit the data that summarizes in tabular format the risk analysis and risk mitigation measures taken to respond to the hazard.

## 7. Manufacturing Information

### 7.1 Information on Manufacturing Process and Manufacturing Site

- (1) State the processes from the acceptance to the release of the component etc. (refers to the “Components” as stipulated in Article 2, Paragraph 2 of the Ministerial Ordinance on Quality Management System for Medical Devices and *In Vitro* Diagnostics [the Ministry of Health, Labour and Welfare Ordinance No. 169 of 2004][CH2]). If procedures has been established to ensure the conformity to the requirements of purchased Components but the purchased Components are not verified based on such procedures, or when the Components are included in the Appendix Table 5 of the Regulations for Enforcement of the Pharmaceutical Affairs Law (the Ministry of Health and Welfare Ordinance No. 1 of 1961[CH3]), then also provide the manufacturing process of the Components. When the Components have been registered pursuant to Article 14-11, Paragraph 1 of the Law (hereinafter referred to as “Master File Registration”), then the name of the manufacturing site for the Components may be provided in lieu of the manufacturing process.
- (2) Also describe the inspection items in each process for inspections on work in process and finished products.
- (3) If the quality, property, etc. of the product varies depending on the manufacturing conditions, then state the manufacturing conditions of any process that has a large impact on the quality or safety of the medical device for which approval is sought.
- (4) As the manufacturing site information, provide the name, address, license or accreditation number, and license or accreditation category for primary licensed manufacturer, and if applicable, licensed sterile medical device manufacturer, licensed cell/tissue engineered medical device manufacturer, and licensed labeling manufacturer of the medical device indicated on the application form to correspond to the process flowchart.
- (5) When an external testing laboratory is used, provide the outsourced inspection items, and also the name and address of the laboratory.
- (6) State the name and address of the business establishment that performed the primary design of the product, and explain the relationship with the applicant (including a summary of the contract).
- (7) If the applicant intends to obtain approval for distributing a component of the medical device as a single part, and when the manufacturing method and quality inspection items for the component are different from the descriptions above, such information must also be stated.
- (8) When incorporating a component that by itself has been approved or certified as a medical device or for which a marketing notification has been submitted, state the name of the marketing authorization holder of the component, address of its main business establishment, license number of the marketing authorization holder, approval number

or certification number, brand name and product name in the section where the component is indicated.

- (9) If the Components of the medical device has been registered in the Master File, state the name and address of the supplier of the Components, the name and address of the manufacturing site, Master File registration number, and, if the manufacturing site is required to have a license for manufacturing medical devices, then the license category, license number, and license date, in the section where the Components are indicated. If the Master File Registration application is pending, make a note to that effect.

## 7.2 Sterilization Method

- (1) Provide an outline of each validation that served as the rationale for establishing the sterilization conditions, and state the sterilization conditions such as sterilization parameters.

Also, state the rationale for the judgment that the tests performed are necessary and sufficient to evaluate the sterilization method based on the current levels of scientific and technical knowledge.

- (2) If a test does not meet the requirements stipulated in the Japanese sterilization validation standards (PMSB/CND [*Iyakukan*] Notification No. 1 by the Director of Compliance and Narcotics Division, dated July 1, 1997, “Sterilization Validation Standards”), guidelines on sterilization validation (PMSB/MDD [*Yakuki*] Notification No. 60 by the Director of Medical Device Division, dated March 31, 1997, “Guidelines on Basis for Establishing the Radiation Sterilization Dose for Medical Devices”, and PMSB/CND [*Iyakukan*] Notification No. 69 by the Director of Compliance and Narcotics Division, dated May 1, 1998, “Guidelines on Sterilization Validation of Medical Devices”), etc., state the section where the test does not meet the requirements, the reason for the discrepancy, and the justification for the test.

- (3) If a bovine-derived material is used, state the country of origin of the raw material, the body part, processing method, and, as necessary, information on the TSE data and other information that is necessary from a perspective of ensuring quality and safety.

In addition, when using a human- or animal-derived material, clarify the validity of the origin (including details of donor screening), and describe the tests on validation of removal or inactivation methods of viruses and other pathogens in the manufacturing process.

## 7.3 Quality Control

As the information on quality control, explain the purpose of inspection and a summary of the procedures for the inspection items described for the manufacturing process in Section 7.1, and explain the relationship of those to the product specifications proposed in the application form for each inspection item.

## Annex 1

### Format of Summary Technical Documentation

1. Summary of Product
  - 1.1 Overview of Product
  - 1.2 Origin or History of Discovery and History of Development
  - 1.3 Usage Conditions in Foreign Countries
2. Essential Principles and Conformity to Essential Principles
  - 2.1 List of Referenced Standards
  - 2.2 Essential Principles and Evidence of Conformity
3. Device Description
  - 3.1 General Information
  - 3.2 Raw Materials
  - 3.3 Product Specifications
  - 3.4 Storage Method and Expiration Period
  - 3.5 Comparison with Similar Medical Devices
4. Summary of Pre-clinical Design Verification and Validation Documents
  - 4.1 General Information
    - (1) Declaration of Conformity to Standards
  - 4.2 Summary of Medical Device Design Validation
    - 4.2.1 Tests to Support Safety
      - (1) Physical and Chemical Properties
      - (2) Electrical Safety and Electromagnetic Compatibility
      - (3) Biological Safety
      - (4) Radiation Safety
      - (5) Mechanical Safety
      - (6) Stability and Durability
    - 4.2.2 Tests to Support Performance
    - 4.2.3 Tests to Support Efficacy
    - 4.2.4 Tests to Support Usage Method
  - 4.3 Clinical Evidence
    - (1) Clinical Trial Results
    - (2) Conclusion of Clinical Trial Results
    - (3) Miscellaneous
5. Labeling
  - 5.1 Instructions for Use (Draft) and Basis for Establishing Its Content
  - 5.2 Label (Draft)
6. Risk Analysis

6.1 Risk Analysis System

6.2 Important Hazards

7. Manufacturing Information

7.1 Manufacturing Process and Manufacturing Site

7.2 Sterilization Method

7.3 Quality Control



## Annex 2

## Overview of Product

1	Category		
2	Name	Generic name	
		Brand name	
3	Classification		
4	Name of applicant		
5	Intended use, Indications		
6	Structure and principle		
7	Operation or usage method		
8	Note	Date of Application Application category Explanation of innovativeness	

## Note:

- In the “Classification” column, provide the class as specified by the classification in the Notification by the Director-General of Pharmaceutical and Food Safety Bureau, dated July 20, 2004, “Implementation of Specially Controlled Medical Devices, Controlled Medical Devices and General Medical Devices Specified by the Minister of Health, Labour and Welfare According to the Provisions of Article 2, Paragraphs 5 to 7 of the Pharmaceutical Affairs Law and (Ministerial Notification) and Specially Designated Maintenance and Management Required Medical Devices Specified by the Minister of Health, Labour and Welfare According to the Provisions of Article 2, Paragraph 8 of the Pharmaceutical Affairs Law (Ministerial Notification).”
- In the “Note” column, concisely describe the date of application, application category, and explanation of innovativeness.