

Provisional Translation (as of March 16, 2009) *

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 Attached to
Application 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, dated January 28, 1999, "Handbook for Preparation of Summary Technical Documentation Attached to Application for Approval for New Medical Devices," the Ministry asked applicants to prepare "Summary Technical Documentation (STED)," which concisely summarizes the attached technical documents. In addition, on a trial basis, the Ministry has accepted Summary Technical Documentation (STED), which has been studied by the Global Harmonization Task Force Conference, as a summary of technical documents according to the PMSB/ELD (*Iyakushin*) Notification No. 0201099 by the Director of Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau, Ministry of Health, Labour and Welfare, dated February 1, 2002, "Trial Acceptance of Summary Technical Documentation (STED) for Approval Evaluation of Medical Devices."

Based on the above developments, the Ministry has made the following decision concerning the evaluation of marketing approval applications for 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

* 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 Japanese text shall prevail.

Collection and Donation Services Control Law (Law No. 96 of 2002). The Ministry will request applicants to prepare a summary of technical documents according to the STED format and to attach the summary of technical documentation to applications for marketing approval, excluding those for medical devices whose approval is evaluated by establishing standards for each generic name and verifying their conformity to the standards. As a guideline for preparing the STED, the Ministry has developed the Handbook for Preparation of Summary Technical Documentation Attached to Application 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 Attached Summary Technical Documentation

The attached summary technical documentation should provide an overview of the medical device for which a marketing approval application is submitted by an applicant, based on the technical documents attached to the application form. It must be prepared by the applicant. The STED accurately and concisely summarizes the flow of development, including the applicant's views and basis for judgment during the development process, and key points on quality, efficacy, and safety, by incorporating the applicant's evaluation of clinical usefulness. 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 the application is submitted.

The STED, which has been newly adopted as a format for a summary of technical documents, was developed by the Global Harmonization Task Force Conference (GHTF). The STED format appropriately summarizes the technical documents that marketing authorization holders or manufacturers of medical devices maintain 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 approval applications.

This handbook is intended to standardize the format and content of summary technical documentation to help applicants streamline their preparation process of the summary technical

documentation while assisting reviewers who evaluate the applications understand the content of summary technical documentation, thereby expediting the evaluation for medical devices, and, at the same time, it contributes to the improvement of evaluation because comparison would be easier to make between similar medical devices.

This handbook is not designed for technical documents for any particular medical device, but encompasses technical documents in general that must be attached to approval applications. 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 apply to approval applications, excluding those for medical devices that require a preliminary evaluation concerning verification of manufacturing according to the Guidelines for Assurance of Quality and Safety of Drugs Manufactured Using Human-Derived Cells and Tissues (PMSB (*Iyaku*) Notification No.1314 by the Director-General of Pharmaceutical and Medical Safety Bureau, dated December 26, 2000) and medical devices whose applicants claim their conformity to the approval standards.

II. General Points of Consideration

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 layout must be as shown in Annex 1.

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

3. Use serial numbers for each page, and provide a table of contents for the entire summary technical documentation.
4. Following the cover page, insert the form shown in Annex 2 to show an outline 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 summary technical documentation.
5. In principle, allocate one or two pages for “Executive Summary” for each category of summaries of design verification and design validation, and provide a summary for the entire test in the category and the applicant’s view (1 or 2 pages). After the “Executive

Summary,” provide an outline of the test method and test results for each test in the category, and provide the necessary discussion. In this case, use tables and figures, whenever possible.

6. To provide appropriate description, make sure to clearly distinguish relevant facts based on technical documents from the applicant's views or interpretations. When the facts are based on technical documents, clearly distinguish the attached technical documents from reference documents.
7. Clarify the relationship between the content of summary technical documentation and the corresponding attached technical documents to allow the reviewers to promptly and accurately find the relevant section in the summary technical documentation.

To this end, it is recommendable that the applicant print the technical document number in an upper corner of each page. If the attached technical documents constitute 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 approval standards, guidelines, etc. established by the Ministry of Health, Labour and Welfare are available, clarify whether the test was conducted according to those standards or guidelines. If the test deviates from the standards or guidelines, state the sections, the reason and justification for the deviation. The same procedures will apply to such standards as Japan Industrial Standard (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 summary technical documentation.
11. In addition to the above, take the following points into account.
 - (1) Use headings and subheadings whenever possible, and itemize whenever 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 the 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 technical document 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 summary technical documentation, clarify the section being quoted.
- (11) When quoting other documents, list the documents in a bibliography 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 estimation and interval estimation, as necessary. Illustrate analytic results, whenever possible.
- (13) If an assay has been conducted, show the assay method. If the assay results are significant, use appropriate symbols to indicate the significant level. If the results are complicated, add explanation or otherwise facilitate understanding.
- (14) Provide the default value, as necessary.

[Attachment]

Handbook for Preparation of Summary Technical Documentation Attached to
Application for Marketing Approval for Medical Devices

1. Executive Summary 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 Course of Discovery and Course 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 any problem arises in the development process or the development plan is changed, 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 any problem arises in the development process or the plan is changed during the development process, 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, approval application format, 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 the application is submitted, but model, energy output, applicable body part, or intended use is different from those for the medical device for which the application is submitted, then provide a summary thereof.

1.3 Usage Status Overseas

- (1) Show the license and usage status overseas, 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 cases where application for license is pending.
- (2) As for malfunctions that have previously been reported in the use in foreign countries, provide an outline of the type of malfunction and frequency of occurrence in a list format.
- (3) If the medical device is not used in a country that imports the medical device, 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 summary technical documentation has been prepared. In particular, if a decision is made on whether a license is granted or denied in major countries where application was pending or when there is a change in the frequency 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 summary technical documentation 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 status in Japan and occurrence of malfunctions in Japan.

2. Essential Principles and Conformity to Essential Principles

2.1 List of Reference Standards

- (1) List the standards that are used to show conformity to the standards for medical devices 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 Essential Principle. The test records or test results that are used to explain conformity to the Essential Principles are provided under the section 4. Design Verification and Design Validation Documentation Summaries, the section 6. Results of Risk Analysis, and the section 7. Manufacturing Information. Indicate where the test records or test results are provided for each Essential Principle.

In addition, explain 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 would 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 package insert.
- (3) Copy the illustration of the device and the description for the features of functions of each part from the Appendix (Form, Structure, and Principle) of the application form.
- (4) If the medical device is medical electrical equipment, copy the principle of the device, including the principle of controls, from the Appendix (Form, Structure, and Principle) of the application form.
- (5) Describe the operation method of the device based on the "Operation Method or Usage Method" column on the application form.
- (6) Explain that the device for which the application is submitted 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 approval 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 the application is submitted, based on the Essential Principles and other reference standards. When adopting appropriate standards, whether domestic or overseas, provide the scientific justification for adopting such standards.

Also, state the reason 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 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 Date

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

3.5 Comparison with Similar Medical Devices

(1) State the efficacy, safety, product features, etc., focusing on differences revealed through comparisons with similar approved medical devices 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 approved medical devices, select those that are similar in terms of intended use, product specifications, usage method, etc. Using the latest package inserts, 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 method 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 structure and principle, raw materials, and product specifications.

Also, state the sources of technical documents for the medical device used for the

comparison.

- (3) Follow the rules below when preparing the list as stipulated under (2).
 - 1) When there is more than one control medical device, list in the order starting from the most recently approved, licensed, or notified medical device.
 - 2) State the re-examination and re-evaluation dates for medical devices for which re-examination and re-evaluation have been completed.
 - 3) If a comparative clinical trial (including blind studies) using a control device has been performed, in principle, enter in the list the medical device used as a control device following the medical device for which the application is submitted, and in the “Note” column, state the type of comparative clinical trial and make a note that the medical device was used as a control device in the study.

4. Summary of Design Verification and Design Validation Documents

4.1 General Information

4.1.1 Declaration of Conformity to Standards

Declare that the item is manufactured to conform to the Essential Principles and the GMP for Medical Devices. The declaration must separately be attached as a STED document. The applicant is advised to prepare the declaration according to ISO 17050-1 “Conformity Assessment - Supplier’s Declaration of Conformity - Part 1: General Requirement.”

4.2 Summary of Medical Device 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 and other safety issues), and describe tests listed as the rationale for conformity to the Essential Principles (excluding clinical trials). Refer to the primary points to consider that are provided in sections 4.2.1 and thereafter.

If a marketing authorization holder or manufacturer’s conformity to the above standards has been certified by a laboratory, which is recognized by a certification body belonging to IAF to conform to the “General Requirements for the Competence of Calibration and Testing Laboratories” (ISO 17025) specified by the International Organization for Standardization, or a laboratory registered according to Article 57, Paragraph 1 of the Industrial Standardization Law (Law No. 185 of 1949) (hereinafter referred to as “JNLA” accreditation), 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 Studies to Support Device Safety

(1) For “Executive Summary,” provide the study items, study method, study results, study sites, technical document number, etc. of studies to support safety in a list, and also provide an outline for each study.

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

(2) In “Executive Summary,” also discuss the relationship between the results of the studies to support safety and product specifications of the medical device for which the application is submitted.

In addition, as necessary, state the clinical positioning and features of the medical device when compared to similar medical devices.

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

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

4.2.1.1 Physical and Chemical Properties

For “Executive Summary,” describe the established test items and 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, extrables, surface properties, etc. according to the properties of the material.

When establishing 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 “Executive Summary,” provide the test items, test method, testing conditions, reference values, test results, testing facility, technical document number, etc. of

electrical safety and electromagnetic compatibility tests conducted in a concise list, 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 “Executive 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 and background for 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 area 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

- (1) For “Executive Summary,” provide a concise list of test items, test methods, test results (e.g., positive, negative, IC50 value, histopathological examination results), testing facility, and technical document number for the biological safety tests that have been 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 “Executive 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 opinions and evaluation for each test.
 - 2) Discuss the justification for an animal experiment model in connection with clinical use on 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 area 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

- (1) For “Executive Summary,” provide a concise list of test items, test method, testing conditions, reference values, test results, testing facility, and technical document number for the radiation safety tests that have been conducted, and also provide an outline for each test.

Also, state the reasons 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 “Executive 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 conformity to laws concerning medical devices such as Chapter 4, Section 2 of the Enforcement Regulations of the Medical Service Law (the Ministry of Health and Welfare Ministerial 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 area 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 “Executive Summary,” provide a concise list of test items, test method, testing conditions, reference values, test results, testing laboratory, and technical document number for the mechanical safety tests that have been 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 “Executive 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) If the medical device is medical electrical equipment, and its 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 “Executive 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 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 test conditions, measured items, and storage period of 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 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 Device Performance

- (1) For “Executive Summary,” provide a list of test items, test method, test results, testing laboratory, and technical document number for the tests that support performance, and also provide an outline for each test.

Also, state the reasons 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 “Executive Summary” the relationship between the results of the test to support performance and the product specifications described in the application. Also, state the medical device’s clinical positioning and features 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 Studies to Support Efficacy

- (1) For “Executive Summary,” provide a list of study items, study method, usage method (dosage and administration), duration of use, control device, study results, study sites, and technical document number for the studies to support efficacy and studies on mechanism of action, and also provide an outline for each study.

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 “Executive Summary,” state the course of investigating the mechanism of

action, as well as the relationship of the results of the studies to support efficacy and the studies on mechanism of action to the efficacy and effect described in the application.

Also, state clinical positioning and characteristics 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 study methods and study results for each study, summarize the findings, and add necessary discussions.
- (4) Use figures and tables to explain test results, whenever possible.

4.2.4 Studies to Support Usage Method

- (1) For “Executive Summary,” provide a list of study items, study method, usage method (dosage and administration), study results, study sites, and technical document number for the studies to support the usage method, and also provide an outline for each study, and state the basis for establishing the usage method, volume used, etc.

Also, state the rationale of the judgment that the study items performed are necessary and sufficient to evaluate the usage based on the current levels of scientific and technical knowledge. Also, 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 study methods and study results for each study, summarize the findings, and add necessary discussions.
- (3) Use figures and tables to explain study results, whenever possible.

4.3 Clinical Evidence

- (1) For “Executive Summary,” provide a list of study types (e.g., comparative clinical or general clinical trials), target patients, number of cases, usage method (dosage and administration), examination and observation items, duration of use, clinical trial period, name of representative study site, and technical document 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 properly.

4.3.1 Clinical Trial Results

- (1) For each study, state the study method (e.g., study objectives, study type, subject inclusion criteria, exclusion criteria, number of cases, 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 in a list, provide the rationale for establishing the subject inclusion criteria, exclusion criteria, and usage method (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, period of illness, 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 frequency by tests and malfunction types, a list of frequency by background factors and malfunction types, 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 for 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 provide their summary. 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 medical device, taking the physician's judgment into account.

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

4.3.2 Conclusion of Clinical Trial Results
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(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 “Clinical Trial Results,” and provide a conclusion.

4.3.3 Miscellaneous

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

5. Labeling

5.1 Package Inserts (Draft)

(1) Provide the package insert (draft) and technical documents that show the rationale for establishing it.

(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 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 “Class Category 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 whose malfunction is relatively likely to endanger the patient’s life, then make quotations from the package inserts, in particular, used in major countries and compare those package inserts with the Japanese one. Also, add the applicant’s discussion.

(3) If precautions are added to the package insert 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” of the package insert (draft), and describe the rationale for the intended use, indications based on a summary of study results that support the efficacy, study results that support the performance, and clinical trial results.

- (5) Enclose in a box the “Operation Method or Usage Method” of the package insert (draft), and describe the rationale for the operation method or usage method based on a summary of study results that support the usage method, study results that support the performance, and clinical trial results.
- (6) Enclose in a box the WARNING and CONTRAINDICATIONS and PRECAUTIONS in the package insert (draft). For each item in the package insert, state the rationale for establishing the information based on non-clinical trial 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 refer to precautions adopted in major countries in which the medical device is used and explain the basis for establishing the information.

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) Pertaining to risk analysis for a medical device, refer to JIS T 14971 “Medical Devices - Application of Risk Management to Medical Devices” to attach technical documents 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. Attach a technical document that summarizes 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 the application is submitted) against which the Ministry of Health, Labour and Welfare requested applicants 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, attach a technical document 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 “Good Manufacturing Practice and Quality Management System at Manufacturing Sites of Medical Devices and In Vitro Diagnostics” [the Ministry of Health, Labour and Welfare Ministerial Ordinance No. 169 of 2004; hereinafter referred to as “Ministerial Ordinance on GMP for Medical Devices”]). 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 Table 5 of the Appendix to the Regulations for Enforcement of the Pharmaceutical Affairs Law (the Ministry of Health, Labour and Welfare Ministerial Ordinance No. 1 of 1961; hereinafter referred to as the “Enforcement Regulations”), then also provide the manufacturing process of the Components. When the Components have been registered according 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 for each process for inspections on work in process and final 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 the application is submitted.
- (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 approval application form to correspond to the process flowchart.
- (5) When an external testing/inspecting institution is used, provide the outsourced inspection items, and also the name and address of the institution.
- (6) State the name and address of the business establishment that performed the primary design of the item, 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 if the manufacturing method or quality inspection for the component is different from the description 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 product notification has been submitted, state the name of marketing authorization holder for 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 and 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 device, then the license category, license number, and license date, and if the Master File registration application is pending, make a note to that effect, in the section where the Components are indicated.

7.2 Sterilization

- (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 reasons that the test items performed are necessary and sufficient to evaluate the sterilization 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, “Standards on Basis for Establishing the Sterilization Dose for Radiation Sterilization of 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 area 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 TSE technical documents 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 the product specifications established on the approval application form for each inspection item.

Annex 1

Format of Summary Technical Documentation

1. Executive Summary of Product
 - 1.1 Summary of Product
 - 1.2 Origin or Course of Discovery and Course of Development
 - 1.3 Usage Status Overseas
2. Essential Principles and Conformity to Essential Principles
 - 2.1 List of Reference 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 Date
 - 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 Studies to Support Device Safety
 - (1) Physical and Chemical Properties
 - (2) Electrical Safety and Electromagnetic Compatibility
 - (3) Biological Safety
 - (4) Radiation Safety
 - (5) Mechanical Safety
 - (6) Safety and Durability
 - 4.2.2 Tests to Support Device Performance
 - 4.2.3 Studies to Support Efficacy
 - 4.2.4 Studies to Support Usage Method
 - 4.3 Clinical Evidence
 - (1) Clinical Trial Results
 - (2) Conclusion of Clinical Trial Results
 - (3) Miscellaneous
5. Labeling
 - 5.1 Package Insert (Draft) and Basis for Establishing Its Contents
 - 5.2 Label (Draft)
6. Risk Analysis

6.1 Risk Analysis System

6.2 Serious Hazards

7. Manufacturing Information

7.1 Manufacturing Process and Manufacturing Site

7.2 Sterilization

7.3 Quality Control

Annex 2

Summary of Product

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

Note:

- In the “Class category” column, provide the class in the class category 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 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 application date, application category, and explanation of innovativeness.