

December 7, 2011

Attn: Directors of Prefectural Public Health Departments/Bureaux

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

Re: Publication of the Guidance for the Evaluation of Emerging Technology Medical Devices

The Ministry of Health, Labour and Welfare of Japan intends to establish a guidance for the evaluation of emerging technology medical devices, for which there is a high demand in clinical practice, by selecting the target areas to be studied in order to facilitate efficient product development and speed up the approval process through the advance preparation and publication of documents, such as a guidance for technical evaluation, to be used for the review.

Here, we present the guidance comprising the documents that may be required for the evaluation of cell sheets used in the regeneration of periodontal tissue, orthopedic customized artificial hip joint prostheses and computer-aided diagnostic devices, and the advice for evaluation. We would like your cooperation in promulgating this guidance among the relevant vendors and service providers under your jurisdiction for use as a reference when filing an application for manufacturing/marketing approval. Attention should be paid to the following points.

(For your reference, copies of this notification will also be sent to the Chief Executive of the Pharmaceutical and Medical Devices Agency, Chairman of the Japan Federation of Medical Devices Associations, Chairman of the American Medical Devices and Diagnostics Manufacturers' Association, and the Chairman of the Medical Equipment Committee of the Council of the European Business Community in Japan.)

1. The guidance makes recommendations regarding points that should be considered in product evaluation (evaluation items) from the viewpoints of collecting application documents for approval and accelerating the review process. The guidance is not

positioned as a legal standard but is designed simply to suggest currently recognized evaluation items for emerging technology medical devices. It has to be noted that other kinds of evaluation may be needed, or there may be some exceptions to this guidance depending on the product characteristics.

2. When collecting documents and data required for submission of an application for approval of individual products, it is recommended that the issues presented in the guidance be discussed in advance, and to use the consultation service of the Pharmaceutical and Medical Devices Agency at the earliest possible opportunity.

Guidance on Evaluation of Orthopedic Customized Artificial Hip Joint Prosthesis

1. Introduction

In the field of orthopedics, implants (classified as “medical devices” by the Pharmaceutical Affairs Law) have been used widely as ready-made implants due to their proven mechanical and biological safety and efficacy, and have contributed to the improvement in the quality of medical care and the lives of people in Japan. However, in clinical practice, bone structure and geometry vary among individual patients, and there are reports of cases where ready-made implants cannot be used effectively. Therefore, there is a compelling need for implants with greater compatibility for individual patients, so-called customized implants, as a solution to the problem of biological incompatibility.

Because customized implants are compatible with individual patients, they are expected to play a major role in the introduction of bone preservation therapies, ensuring compatibility and stability, implementation of less invasive surgical procedures, successful functional reconstruction, improvement of implant service life, early rehabilitation and reentry into society, and reduction in the need for revision surgery. In other words, it will be beneficial not only for patients and medical workers but also in terms of medical economics to have the needs of patients and medical workers satisfied and to secure excellent clinical results through the clinical adoption of customized implants that meet the requirements of individual patients. As technological innovation has made marked advances and made it possible to produce customized implants that meet such clinical needs, it is now feasible to produce safer implants with better biocompatibility.

Customized implants are expected to be used for applications such as joint prostheses and devices for osteosynthesis. In clinical practice, joint prostheses (e.g., artificial hip joint, knee joint, shoulder joint, and elbow joint) are typical examples of applications that require customized implants optimally shaped to fit various bone geometries and accommodate serious bone defects and/or deformations. This guidance is designed to specify the requirements for customized artificial hip joint prostheses for which there is a high demand in clinical practice.

2. Scope

Among orthopedic implants, the scope of this guidance is artificial hip joint prostheses (including femoral head prosthesis). In this guidance, a customized artificial hip joint prosthesis is defined as an artificial hip joint prosthesis with improved biocompatibility and stability achieved through minimal modification to the shape of a ready-made prosthesis in order to match the bone geometry of an individual patient for whom a ready-made prosthesis is not suitable.

3. Role of This Guidance

In consideration of the fact that the scope is orthopedic artificial hip joint prostheses (including femoral head prosthesis) that are being developed based on the remarkable technological advances occurring in this area, this guidance is designed to indicate current issues instead of providing a comprehensive list of problems and points to consider. Therefore, it will be revised as technological innovation progresses and knowledge accumulates, and it does not mandate what information must be included in application documents for approval.

For the evaluation of customized artificial hip joint prostheses, it is necessary to have a thorough understanding of the characteristics of individual products and to handle the data in a flexible and scientifically rational manner.

It is also recommended that other relevant guidelines from both Japan and overseas should be consulted in addition to this guidance.

4. Contents of Written Application for Approval of Customized Artificial Hip Joint Prosthesis

(1) Form, Structure and Mechanism

In the section “Form, Structure and Mechanism,” specify the dimensional ranges in which the customized artificial hip joint prosthesis can be produced, separately from the ready-made prosthesis upon which the production of customized prosthesis is based.

(2) Purpose of Use, Indications or Efficacy

In the section “Purpose of Use, Indications or Efficacy,” specify that the customized artificial hip joint prosthesis is to be used in the following cases:

- 1) When a physician judges that a sufficient therapeutic effect cannot be obtained with a ready-made prosthesis.
- 2) When a physician judges that a more significant therapeutic effect can be obtained with a customized artificial hip joint prosthesis than with a ready-made prosthesis.

(3) Product Specifications

In terms of production and structure, specify the technological reference data showing that the performance of the customized artificial hip joint prosthesis is equivalent to or higher than that of the corresponding ready-made prosthesis.

(4) Other

- 1) Specify the data of the ready-made prosthesis used as the basis for producing the customized artificial hip joint prosthesis.
- 2) Attach the draft specification form prepared by a physician.

5. Evaluation of Customized Artificial Hip Joint Prosthesis

(1) Evaluation of Production Technology

Specify that the production technology is equivalent to that of the corresponding ready-made prosthesis, or equivalent or superior to that of other ready-made prostheses made or supplied by your own company and which have already been approved.

(2) Evaluation of Safety

Specify that the basic safety profile (e.g., biological safety) of the materials needed to produce the customized artificial hip joint prosthesis is equivalent or superior to that of the corresponding ready-made prosthesis. Submission of safety data on customized prostheses can be omitted if its safety can be proven using the data and scientific evidence for ready-made prostheses. When it is determined that high functionality and durability are needed in clinical practice, submit the data and the scientific basis for similar biomaterials approved for use in artificial hip joint prostheses.

(3) Evaluation of Mechanical Safety

Submission of mechanical safety data can be omitted if data are presented to show that the dimensions of the customized artificial hip joint prosthesis are within the range of the corresponding ready-made prosthesis, or that the mechanical safety is not inferior to that of the corresponding ready-made prosthesis.

It is possible to show that the mechanical safety is not inferior to that of ready-made prosthesis by the following methods:

- 1) When the customized artificial hip joint prosthesis is modified to make it mechanically safer than the corresponding ready-made prosthesis, mechanical safety testing can be omitted by specifying it using the Appendix listing items to be customized as a reference (test data on approved products made or supplied by your own company can also be used).
- 2) When it is necessary to modify sites subjected to a structural load, specify that mechanical safety can be guaranteed based on a mechanical test performed in accordance with some other guideline (test data on approved products made or supplied by your own company can also be used).

6. Preparation and Actions by Marketing Authorization Holder

The marketing authorization holder shall prepare the documents stipulated in the Ordinance on Standards for Manufacturing Control and Quality Control of Medical Devices and in vitro Diagnostic Drugs (MHLW Ministerial Ordinance No.169, 2004, “QMS Ordinance”), Ordinance on Standards for Quality Assurance for Drugs, Quasi-drugs, Cosmetics and Medical Devices (MHLW Ministerial Ordinance No.136, 2004, “GQP Ordinance”), Ordinance on Standards for Post-marketing Safety Management for Drugs, Quasi-drugs, Cosmetics and Medical Devices (MHLW Ministerial Ordinance No.135, 2004, “GVP Ordinance”), or the Ordinance on Standards for Post-marketing Survey and Examination of Medical Devices (MHLW Ministerial Ordinance No.38, 2005, “GPSP Ordinance”), and specify in the documents the following information in order to comply with these requirements.

(1) Design of Customized Artificial Hip Joint Prosthesis

The marketing authorization holder shall design a customized artificial hip joint prosthesis within the range that has been approved in accordance with the written specifications prepared by a physician.

(2) Documents to be Retained by Marketing Authorization Holder

The marketing authorization holder shall keep the following documents related to the production of a customized artificial hip joint prosthesis and selling/offering it to the physician who prepared the written specifications.

- 1) Name of the physician who prepared the written specifications
- 2) Written specifications prepared by the physician (including data on the patient's bone geometry)
- 3) Documents to verify that the design is compatible with the data on bone geometry
- 4) Documents to show that the physician confirmed that the product shape conforms to the written specifications at the design stage or after the final product was made.

(3) Evaluation of Efficacy

The marketing authorization holder shall evaluate the clinical efficacy of the customized artificial hip joint prosthesis by comparing it with the patient's bone geometry before and after implantation, in collaboration with the physician.

(4) Post-marketing Survey

After implantation of the customized artificial hip joint prosthesis, the marketing authorization holder shall collect information on clinical outcomes and adverse events in cooperation with the physician. If necessary, a partial change application or safety measures should be taken.

7. Precautions for Use

The marketing authorization holder shall specify the following information in the section "Precautions for Use" or other sections.

- 1) The customized artificial hip joint prosthesis can be used only when the physician judges that the patient will not gain a sufficient therapeutic effect with a ready-made

prosthesis, or that the patient will have a significantly better therapeutic effect compared to a ready-made prosthesis.

- 2) The patient shall be provided with the information on the need for and clinical efficacy of a customized artificial hip joint prosthesis and give informed consent.
- 3) The attending physician shall prepare the written specifications before using a customized artificial hip joint prosthesis.
- 4) The physician shall submit the written specifications to the marketing authorization holder in order to clarify the items to be customized.
- 5) Before using the customized artificial hip joint prosthesis, the physician shall verify whether the customized artificial hip joint prosthesis meets the written specifications at the design stage or after the final product was made.
- 6) The physician shall take precautions by, for example, preparing a surgical plan that takes into consideration the option of using a ready-made prosthesis in situations where the customized artificial hip joint prosthesis cannot be used due to a product defect or clinical problem that arises during surgery.
- 7) The physician shall evaluate the clinical efficacy and collect information on adverse events in order to provide the information promptly to the marketing authorization holder.
- 8) Because the customized artificial hip joint prosthesis is designed to fit an individual patient, unused products must not be used for other patients.
- 9) The physician shall ensure that the written specifications are retained with the patient's medical records.

Appendix. Items to be Customized

1. Acetabular Components

(1) Acetabular Shell (Socket)

- Shaping (partial increase in volume aiming to achieve compatibility with bone geometry, improved support of marginal area, increased thickness, optimized diameter, optimized curvature of bone-contacting surface, and optimized area of surface treatment)
- Optimized position, number and shape of screw holes
- Optimized position and number of spikes, pegs, and fins

(2) Cementless Polyethylene Liner

- Shaping of polyethylene material (optimized shape of marginal area and polyethylene material)

(3) Cemented Polyethylene Socket

- Shaping of polyethylene material (optimized shape of marginal area, etc.)

2. Femoral Stem

(1) Proximal Area

Cementless stem

- Shaping (optimized shape of parts in the superolateral, superomedial, superoanterior and superoposterior areas and collar shape to achieve compatibility with bone geometry)
- Optimized area of surface treatment to achieve compatibility with bone geometry
- Optimized neck length, neck-shaft angle, and anteversion angle

Cemented stem

- Shaping (optimized shape of parts in the superolateral, superomedial, superoanterior and superoposterior areas and collar shape to achieve compatibility with bone geometry)
- Added surface treatment (optimized area needed to achieve cement fixation)
- Optimized neck length, neck-shaft angle, and anteversion angle

(2) Distal Area

Cementless stem

- Shaping (optimized length, diameter and curvature of the distal area to achieve

compatibility with bone geometry)

- Added surface treatment (optimized area needed to achieve bone induction/conduction)
- Optimized position and size of locking screw holes on the stem side and screw holes for greater trochanter fixation

Cemented stem

- Shaping (optimized length, volume and curvature of the distal area to achieve compatibility with bone geometry)
- (3) Optimized biocompatibility and durability required for sites on which structural load is applied
- Mechanical safety shall be guaranteed (safety to the level approved for ready-made prostheses shall be guaranteed)