

To: 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

Publication of Guidance for the Evaluation of Emerging Technology Medical Devices/Regenerative Medical Products

The Ministry of Health, Labour and Welfare of Japan has sought to establish guidance for the evaluation of selected emerging technology medical devices/regenerative medical products for which there is a high demand in clinical practice, to facilitate efficient product development and speed up the approval process of them through the advance preparation and publication of guidance, instructing technical standards used for the review.

Here, we present a guidance comprising the data and documents that may be required for the evaluation of orthopedic custom-made artificial knee joint prostheses and RNA profiling-based diagnostic equipment, 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, the Chairman of the Medical Equipment Committee of the Council of the European Business Community in Japan, and other related associations.)

1. The guidance makes recommendations regarding points that should be considered in product evaluation (evaluation items) from the viewpoints of collecting the data and documents for approval and accelerating the review process. The guidance is not positioned as a legal standard but is designed to present simply currently recognized evaluation items for emerging technology medical devices/regenerative medical products. It has to be noted that kinds of evaluation may be needed, or there may be some exceptions to this guidance need not be applied depending on the product's characteristics.
2. When collecting documents and data required for submission of an approval application 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 (PMDA) at as early a stage as possible.

Guidance on Evaluation of Orthopedic Custom-made Artificial Knee Joint Prosthesis

1. Introduction

In the field of orthopedics, implants (classified as “medical devices” by the Pharmaceutical Affairs Law) have been used widely in clinical practice and contributed to the improvement of the quality of medical care and the lives of people in Japan. There are, however, reports of clinical cases in which approved implants cannot be used effectively because of a significant deviation in the bone geometry of the affected joint, significant bone defects or deformations, and/or a re-implantation. To meet these clinical needs and solve the issues, so-called custom-made implants are needed.

The use of custom-made implants is expected to provide various benefits due to their great compatibility for individual patients, such as realization of bone-conserving treatment, acquisition of adequate compatibility and fixation, realization of minimally invasive surgery, superior functional restoration, improvements in endurance, early initiation of rehabilitation exercise and early reentry into society, and reduction in the need for revision surgery. In particular, the knee joint is a bodily tissue indispensable for some base functions for human life such as the support of the trunk and the securement of ambulation; better clinical outcomes that may be achieved with custom-made artificial knee joint prostheses may therefore be beneficial for patients and healthcare workers as well as in terms of medical economics.

The significant advancements in the technology that allows for manufacturing custom-made artificial knee joint prostheses have made it possible to produce safer implants with better biocompatibility.

This guidance establishes the requirements regarding the quality, efficacy, and safety of custom-made artificial knee joint prostheses, the products highly needed in clinical practice, and considerations in applying for marketing approval of those products.

2. Scope

This guidance covers, among orthopedic implants, artificial knee joint prostheses excluding unicompartamental ones. In this guidance, a *custom-made artificial knee joint prosthesis* is defined as an artificial knee joint prosthesis with improved biocompatibility and/or improved fixation achieved as a result of minimal modifications made to an approved product according to the bone geometry of the individual patient when incompatible regions exist in the approved product. Re-designs of the sliding surface are not included in these modifications, except when maintaining the geometrical similarity to the approved product.

3. Role of This Guidance

In consideration of the fact that this guidance covers orthopedic artificial knee joint

prostheses (excluding unicompartmental ones), for which technological advancements are being rapidly made, this guidance is not to provide a comprehensive list of issues and considerations but to indicate currently conceivable points. This guidance will therefore be revised as technological innovations are made and knowledge accumulates, and it is not to restrict, e.g., the contents of regulatory submission.

In evaluating custom-made artificial knee joint prostheses, it is required to have a thorough understanding of the characteristics of individual products and with this understanding, to handle the data in a flexible and scientifically rational manner.

Consultation of other relevant guidelines from Japan and overseas should also be considered in addition to the use of this guidance.

4. Contents of Written Application for Approval of Custom-made Artificial Knee Joint Prostheses

In the approval application of a custom-made artificial knee joint prosthesis, the manufacturer should specify the dimensional ranges in which the product can be made by modifying a base approved product (which can be an approved product or a product under simultaneous application).

(1) Geometry, Structure and Mechanism

The dimensional ranges in which the proposed custom-made artificial knee joint prosthesis can be made should be specified in the section “Geometry, Structure and Mechanism” of the application, separately from the description of the base approved product.

(2) Purpose of Use or Indications

In the section “Purpose of Use or Indications” in the application, it should be stated that the custom-made artificial knee joint prosthesis can be used

- 1) when the physician judges that incompatibilities with the approved product prevents the treatment from achieving an adequate effect, or
- 2) when the physician judges that greater therapeutic effects such as improvements in biocompatibility or fixation will be obtained compared with when using the approved product.

(3) Product Specifications

With respect to the manufacturing process and product structure, technical criteria for production that ensure that the performance of the product is equivalent or superior to the base approved product should be described.

(4) Others

- 1) Data for the approved product on which the proposed custom-made artificial knee joint prosthesis is based should be provided.
- 2) A draft Specification Form to be filled out by the physician should be attached.

5. Evaluation of Custom-made Artificial Knee Joint Prostheses

(1) Evaluation of Manufacturing Technique

It should be shown that the manufacturing technique for the proposed custom-made product is the same as that of the base approved product, or equivalent or superior to that of another approved product for which the applicant holds marketing authorization.

(2) Evaluation of Physical and Chemical Characteristics and Biological Safety

It should be shown that the materials used for the production of the custom-made artificial knee joint prosthesis are equivalent or superior to those of the approved product in terms of their biological safety and other relevant characteristics. The need for the studies to evaluate the biological safety may be obviated by showing data of the approved product with a scientific rationale for the use of them. If it is considered that high functionality and/or durability are clinically needed, data of the same kind of biomaterial approved for the use in artificial knee joint prosthesis products should be shown with a scientific rationale.

(3) Evaluation of Mechanical Safety

The need for the studies to evaluate the mechanical safety may be obviated by showing that the dimensions of the proposed custom-made artificial knee joint prosthesis are within the range of the base approved product or that the mechanical strength of the custom-made product is non-inferior to the base approved product.

There may be two approaches to show that the mechanical strength of the custom-made product is non-inferior to the approved product:

- 1) If the custom-made artificial knee joint prosthesis is made by modifying the geometry of the base approved product toward a direction that makes the custom-made product mechanically safer than the approved product, the need for the mechanical safety studies may be obviated by describing it in reference to the Appendix (use of test data of an approved product for which the applicant holds marketing authorization may also be possible).
- 2) If, in the custom-made artificial knee joint prosthesis, improvements are required in some parts that can be structurally stressed, the applicant should show that it is possible to ensure adequate mechanical strength for the product by conducting appropriate studies such as mechanical tests according to relevant guidelines and other references (use of test data of an approved product for which the applicant holds marketing authorization may also be possible).

Appendix. Items to be Customized

Fixed-bearing, cruciate retaining (CR)-type and posterior stabilized (PS)-type are adapted to cementless direct and cemented indirect fixation techniques.

This guidance does not cover mobile-type knee prostheses.

This guidance does not cover the hinge part of hinge-type knee prostheses.

Re-designs of the sliding surface are not included in the customizations considered.

1. Femoral component

Addition of a particular geometry to the femoral component (i.e., addition of a partial structure for a bone defect or another bone irregularity to improve the compatibility with the bone geometry)

Addition of a particular geometry to the bone-implant interface

- i. Optimization of the design of the bone-implant interface (front, front flange, back, and/or proximal designs)
- ii. Optimization of the stem (length, thickness, shape)
- iii. Optimization of pegs (length, thickness, number, shape, position)
- iv. In cementless direct fixation, optimization of the surface treatment area of the back

2. Tibial component

Re-design of the bone-implant interface

- i. Optimization of the design of the bone-implant interface (front, back, inside, outside, and/or distal designs)
- ii. Optimization of the stem (length, thickness, shape)
- iii. Optimization of pegs/fins (length, thickness, number, shape, position)
- iv. Optimization of screw holes (number, position)
- v. In cementless direct fixation, optimization of the surface treatment area of the back
- vi. Optimization of the polyethylene inserts

3. Patellar component

Optimization of the design of the bone-implant interface (thickness, number of pegs, peg position)

4. Parts for filling with a metallic material

These are customizations to add a particular shape by filling a bone deficit with a metallic material.

- i. Optimization of the design of the bone-implant interface
- ii. In cementless direct fixation, optimization of the surface treatment area of the back

6. Preparation and Actions by Marketing Authorization Holder

The MAH must follow the requirements (1)-(4) below:

(1) Design of the custom-made artificial knee joint prosthesis

The MAH is required to design the custom-made artificial knee joint prosthesis within the approved range according to the specifications determined by the physician.

(2) Records to be retained by MAH

In producing a custom-made artificial knee joint prosthesis and selling and providing it to the physician who determines its specifications, the MAH is required to retain the following records based on the Ministerial Ordinance on Quality Management System (QMS) for Medical Devices and In vitro Diagnostics (MHLW Ministerial Ordinance No.169 of 2004), the Ministerial Ordinance on Good Quality Practice (GQP) for Drugs, Quasi-drugs, Cosmetics, and Medical Devices (MHLW Ministerial Ordinance No.136 of 2004), the Ministerial Ordinance on Good Vigilance Practice (GVP) for Drugs, Quasi-drugs, Cosmetics, and Medical Devices (MHLW Ministerial Ordinance No.135 of 2004), or the Ministerial Ordinance on Good Post-Marketing Study Practice (GPSP) for Medical Devices (MHLW Ministerial Ordinance No.38 of 2005):

- 1) Name of the physician who determines the specifications of the prosthesis
- 2) The Specification Form filled out by the physician (including data for the patient's bone geometry)
- 3) Documents ensuring that the prosthesis' design conforms to the bone geometry data
- 4) Documents showing that the physician confirmed that the geometry of the product meets its specifications when the final product was made or during the design of it.

(3) Efficacy Assessment

In applying the custom-made artificial knee joint prosthesis based on specifications determined by a physician to a clinical case, the MAH is required to assess the clinical effectiveness of the customized prosthesis by, in cooperation with the physician, comparing it with the patient's bone geometry before and after implantation.

(4) Post-marketing Survey

After implantation of each customized knee prosthesis, the MAH is required to collect information on its clinical outcomes and malfunctions in cooperation with the physician. The MAH should submit a partial change application and/or implement safety measures, as necessary.

7. Precautions for Use

The MAH should provide the following information in the "Precautions for Use" section (or another appropriate section) of the product's instruction document.

- (1)The custom-made artificial knee joint prosthesis can be used only when the physician judges that any approved prosthesis will not provide an adequate therapeutic effect because of some incompatibilities or that the custom-made artificial knee joint prosthesis will provide a significantly better therapeutic effect (improved compatibility or fixation) compared with approved prostheses.
- (2)The patient must be informed about the need for and clinical effect of the custom-made artificial knee joint prosthesis and give written consent beforehand.
- (3)The treating physician must determine specifications for the custom-made artificial knee joint prosthesis prior to its use.
- (4)The physician should provide the MAH with the specifications that clearly define the items requiring customization.
- (5)The physician must confirm that the custom-made artificial knee joint prosthesis meets its specifications when the final product is made or during the design of it, prior to its use.
- (6)The physician is required to prepare appropriate measures such as preparing a surgery plan with an approved knee joint prosthesis beforehand in case of a situation in which the custom-made artificial knee joint prosthesis cannot be used because of a difficulty such as a malfunction or an intraoperative clinical problem.
- (7)For the custom-made artificial knee joint prosthesis used, the physician is required to evaluate its clinical effectiveness, collect information about malfunctions, and promptly inform the MAH about the information about the evaluation results and the malfunctions.
- (8)An unused custom-made artificial knee joint prosthesis made for a particular patient should not be used for another patient because custom-made artificial knee joint prostheses are made so that they are compatible with individual patients.
- (9)The physician must retain a copy of the Specification Form of each custom-made artificial knee joint prosthesis together with patient records including the medical record of the patient.