

December 15, 2010

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 the regeneration of articular cartilage, neurological function restoration devices and customized orthopedic devices for osteosynthesis, 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 Customized Orthopedic Devices for Osteosynthesis

1. Introduction

In the orthopedic field, implantable devices are widely used and contribute to the improvement of medical care and the quality of life of the Japanese people. These devices are ready-made products with defined width, length and thickness, and their mechanical and biological safety as medical devices has to be established in accordance with the Japanese Pharmaceutical Affairs Law. However, each patient has his/her own skeleton and bone geometry, and ready-made devices may not fit their skeletal structure. In such cases, the use of a customized device that can be fully adapted to individual skeletal structure is required. The use of customized devices enables excellent fixation and restoration of function, leading to better surgical outcomes, the implementation of minimally invasive surgery, early rehabilitation, early reentry into society after surgery and a decrease in the risk of revision surgery, thereby bringing benefits to both patients and medical professionals.

The background to the need for customized devices for osteosynthesis is as follows: the purposes of these devices are becoming increasingly diverse; design concepts of these devices are becoming increasingly complex; and the highly developed technology for product structure and surface treatment have enabled the development of highly biocompatible devices. Accordingly, the introduction of devices with better adaptability to the human body has been sought in the orthopedic field. In other words, the adoption of devices that meet the needs of individual patients, namely, customized devices that can be readily adapted to meet the requirements of individual patients, bring not only benefits to patients and medical professionals but also benefits in terms of medical economics by securing better long-term clinical results.

Although customized devices are expected to be used for applications such as devices for osteosynthesis and joint prostheses, the scope of this guidance is limited to devices for osteosynthesis for which the clinical need is particularly pronounced. This guidance is designed to specify the basic requirements for customized devices for osteosynthesis.

Customized devices with proper articular bone geometry and optimal shape to accommodate significant bone loss, bone deformity and other defects are also required for joint prostheses (e.g., total hip, bipolar, total knee, total shoulder, and total elbow). Therefore,

it was considered necessary to further investigate the remaining issues including the range of application, structural and mechanical properties and the three-dimensional structure of these devices.

2. Scope

The orthopedic devices evaluated using this guidance include metallic implantable devices for osteosynthesis such as bone plates, epiphyseal plates, intramedullary nails, compression hip screws (CHS), short femoral nails, and bone nails.

The customized devices evaluated using this guidance include devices created by partly modifying the shape of a ready-made product. These are altered in order to fit the bone geometry of an individual patient, and the specifications for customized devices are required to be stated in the certificate of approval. Therefore, the devices evaluated using this guidance are different from the custom-made prostheses and artificial bones used in the treatment of malignant tumors or for re-implantation as special treatment materials.

This guidance should not be applied to devices which are produced by manufacturing processes that are different from those used for ready-made products.

3. Role of This Guidance

In consideration of the fact that the scope is customized devices 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 devices, 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 Devices

(1) Form, Structure and Mechanism

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

(2) Purpose of Use, Indications or Efficacy

In the section “Purpose of Use, Indications or Efficacy,” specify that the customized device can be used in the following cases:

- i) When a physician judges that a sufficient therapeutic effect cannot be obtained with ready-made products.
- ii) When a physician judges that a more significant therapeutic effect can be obtained with a customized device than with ready-made products.

(3) Other

Write “including customized device” in the remarks field.

5. Evaluation of Customized Devices

(1) Evaluation of Production Technology

Specify that the customized device can be manufactured using the production technology equivalent to that of the corresponding ready-made product.

(2) Evaluation of Safety

Specify the basic safety profile (e.g., biological safety) of the materials needed to produce the customized device. When the data is omitted by submitting the safety information from a previously approved product, explain the reason for the omission.

(3) Evaluation of Mechanical Safety

Specify that the mechanical safety of the device is not inferior to that of the ready-made product. Examples of such methods are as follows:

- i) Specify the mechanical safety by performing a mechanical test or finite element analysis (FEA) in accordance with the guidelines for the product.
- ii) The mechanical safety information can be omitted if data are presented to show that the dimensions of the customized device are within the acceptable range of the corresponding ready-made product.
- iii) If it is obvious that the changes make the customized device mechanically safer than the ready-made product, documents on mechanical safety can be omitted by describing the safety of the ready-made product with reference to following examples:
 - a) Bone plate

- A. Increase in width
- B. Increase in thickness
- C. Change in length
- D. Decrease in number of holes
- E. Change in position of holes (The change of the interval between screw holes in the long axis shall be applied to the direction of both ends. The change in the short axis shall be measured to the center, but the distance between the holes cannot be changed.)

b) Epiphyseal plate

- A. Increase in width
- B. Increase in thickness
- C. Change in length
- D. Decrease in number of holes
- E. Change in position of holes (The change of the interval between screw holes in the long axis shall be applied to the direction of both ends. The change in the short axis shall be measured to the center, but the distance between the holes cannot be changed.)

c) Intramedullary nail

- A. Decrease in length
- B. Increase in diameter
- C. Decrease in curvature of inflection
- D. Decrease in the number of holes for side-locking screws to prevent rotation

d) CHS

- A. Increase in width
- B. Increase in thickness
- C. Change in length
- D. Decrease in number of holes
- E. Change in position of holes (The change of the interval between screw holes in the long axis shall be applied to the direction of both ends. The change in the short axis shall be measured to the center, but the distance between the holes cannot be changed.)

e) Short femoral nail

- A. Decrease in length
- B. Increase in diameter

C. Decrease in curvature at nail part (maximum fitting)

D. Decrease in the number of holes for side-locking screws to prevent rotation

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 Device

The marketing authorization holder shall design a customized device 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 device and selling/offering it to the physician who prepared the written specifications.

- i) Name of the physician who prepared the written specifications
- ii) Written specifications prepared by the physician (including data on the patient’s bone geometry)
- iii) Documents to verify that the design is compatible with the data on bone geometry
- iv) 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 device 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 device, the marketing authorization holder shall assess the suitability of the customized device and collect information on 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.

- i) The customized device can be used only when the physician judges that the patient will not gain a sufficient therapeutic effect with ready-made products, or that the patient will have a significantly better therapeutic effect compared to ready-made products.
- ii) The attending physician shall prepare the written specifications before using a customized device.
- iii) When preparing the specifications, physicians shall ensure that the customized device does not interfere with soft tissues (including nerves, vessels, muscles) or the range of joint movement is not limited, by fitting the bone geometry within the approved range.
- iv) Physicians shall submit the written specifications to the marketing authorization holder
- v) Before using the customized device, the physician shall verify whether the customized device meets the written specifications at the design stage or after the final product was made.
- vi) The physician shall take precautions by, for example, preparing a surgical plan that takes into consideration the option of using ready-made products in situations where the customized device cannot be used due to a product defect or clinical problem that arises during surgery.
- vii) Because the customized device is designed to fit an individual patient, unused products must not be used for other patients.
- viii) Physicians shall evaluate the clinical efficacy of the designed customized device by comparing the bone geometry of the patient before and after surgery.
- ix) When the customized device is used, the physicians shall evaluate the suitability of the

customized device or collect information on adverse events and then promptly report the information to the marketing authorization holder.

- x) The physician shall ensure that the written specifications are appropriately retained with the patient's medical records.