Attn: Directors of Prefectural Public Health Departments/Bureaux

Counsellor of Minister's Secretariat

(for Medical Device and Regenerative Medicine Product Evaluation),

Ministry of Health, Labour and Welfare

(official seal omitted)

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 documents, instructing technical standards used for the review.

Here, we present guidance comprising the documents that may be required for the evaluation of nasal cartilage regeneration (Attachment 1), cardiac catheter ablation equipment (Attachment 2), and custom-made orthopedic implants (Attachment 3), and the advice for evaluation. We would like your cooperation in promulgating these documents 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 application documents for approval   and accelerating the review process. The

guidance is not positioned as a legal standard but are designed to suggest currently recognized evaluation items for the emerging technology medical devices/regenerative medical products. 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's 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 of consultation service of the Pharmaceutical and Medical Devices Agency (PMDA) at the earliest possible opportunity.

Guidance for Evaluation of Three-dimensional Additive Manufacturing Technology-Based, Custom-made Orthopedic Implants Produced from Patients' Image Data

1. Introduction

The Statistics Bureau of the Ministry of Internal Affairs and Communications (MIC) issued a report on trends in the elderly in Japan on September 15, 2014, and described that the population of the elderly (65 years or older) has reached 32.94 million and this accounts for 25.9% of the total population (Statistical Topics No.84, Statistics Bureau, MIC). Aging in Japan is predicted to continue to accelerate. In this situation, cases of motor impairments (osteoarthritis, or femoral neck fracture or spinal compression fracture associated with osteoporosis) in Japan are monotonically increasing, and it has been urgently needed to facilitate sophisticated orthopedic implants such as those for a bone or a joint, including prostheses and osteosynthetic materials used for the treatment of arthropathy, fractures, or orthomorphia, and improve the treatment techniques.

Conventional orthopedic implants have been proved safe and effective, been shown to be durable for 10 to 20 years after implantation, and contributed to the orthopedic treatment and extension of healthy life expectancy. Current issues of implants, however, include the existence of incompatibilities to the bone due to mismatched geometry because conventional implants are supplied in uniform sizes based on a design determined by average bone geometries. Thus, after a long period has passed after implantation, patients can experience complications such as a fracture, a loosened prosthesis, or a breakage, resulting in reimplantation. In addition, reconstruction with an existing implant can be infeasible in some cases when the bone deficit is a result of wide excision of bone tumor or when reimplanting. With this background, to make advancement toward the goal of further extending the healthy life expectancy of the Japanese public and improving the quality of life, development of very-long-life implants with a durability of 30 years or longer is desired. As an approach to achieve this, customization of implants' geometry has been proposed.

Recently, development of several innovative technologies has made it possible to produce custom-made orthopedic implants in small lots (single production) and in a short period of time using three-dimensional additive manufacturing technologies such as electron beam additive manufacturing, laser additive manufacturing, or inkjet printer manufacturing. This necessitates establishment of new standards for review to appropriately and promptly evaluate the safety and efficacy of osteoarticular implants and associated operation-assisting guides that are produced with 3D additive manufacturing. While considerations for the evaluation of the safety and efficacy of orthopedic implants produced through 3D additive manufacturing were included in September 2014 in a Notification, titled Guidance on Evaluation of Orthopedic Implants Produced With Three-

Dimensional Additive Manufacturing (PFSB/ELD/OMDE/CMS Notification 0912 No. 2 issued by the Counsellor of Minister's Secretariat [for Medical Device and Regenerative Medicine Product Evaluation], MHLW, dated September 12, 2014, Attachment 3; hereinafter, referred to as the Counsellor Notification), in the present guidance considerations required when a 3D bone geometry is reproduced from an individual patient's image data in producing a customized implant using a 3D additive manufacturing technique are included.

2. Scope

This guidance covers 3D additive manufacturing technology-based, custom-made orthopedic implants and associated operation-assisting guides (hereinafter, referred to as custom-made orthopedic implants including the guides) made for the purpose of improving the biocompatibility and/or fixation for particular individual patients by geometrically modifying a base ready-made product so that the implant matches the bone geometry of the individual patient. This guidance shows considerations for the design aimed to reproduce a 3D model of a bone or a cartilage-containing joint using each individual patient's image data.

Note that even if the intended custom-made orthopedic implants are to be produced through a process other than 3D additive manufacturing, such as a cutting process, this guidance may still be used as a reference if the production is done by using a 3D model reconstructed from the patient's image data.

3. Role of This Guidance

In recent years, thanks to 3D additive manufacturing, of which potential applications to the production of medical devices have increasingly drawn attention, it has become possible to produce medical devices with a complex geometry even in small lots and in a wide variety of kinds; given this background, this guidance shows possible issues or points that may arise or should be evaluated or considered when designing and producing custom-made orthopedic implants in a way that matches the osseous/cartilaginous geometry of the individual patient using image data of the bone specific to the patient. As a guidance covering an area experiencing significant technological innovations, it 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. Prior consultation with the Pharmaceuticals and Medical Devices Agency (PMDA) is recommended when a regulatory submission is planned for a novel technology that offers a function that may not be included in those assumed in this guidance.

In evaluating custom-made orthopedic implants produced using a 3D additive manufacturing technique or another, it is required to have a thorough understanding of the individual production processes and the characteristics of individual products and

with this understanding, to handle the data in a flexible and scientifically rational manner. It is also necessary to consult other relevant, currently available guidelines from Japan and overseas in addition to this guidance. It should therefore be noted that whether the characteristics of the individual product can be evaluated using available guidance/guidelines or not should be thoroughly considered. For the evaluation of orthopedic implants produced using 3D additive manufacturing, the Counsellor Notification should also be consulted; for the evaluation of custom-made orthopedic implants, the following guidance should also be consulted:

- Publication of Guidance for the Evaluation of Emerging Technology Medical Devices (PFSB/ELD/OMDE Notification 1215 No.1 dated December 15, 2010), Attachment 3 "Guidance on Evaluation of Custom-made Orthopedic Devices for Osteosynthesis"
- Publication of Guidance for the Evaluation of Emerging Technology Medical Devices (PFSB/ELD/OMDE Notification 1207 No.1 dated December 7, 2011), Attachment 2 "Guidance on Evaluation of Orthopedic Custom-made Artificial Hip Joint Prosthesis"
- Publication of Guidance for the Evaluation of Emerging Technology Medical Devices (PFSB/ELD/OMDE/CMS Notification 1120 No.5 dated November 20, 2012), Attachment 1 "Guidance on Evaluation of Orthopedic Custom-made Artificial Knee Joint Prosthesis"

4. Considerations in Reproducing 3D Bone Model from Patients' Image Data

(1) Acquisition of Image Data from Patients

In designing a custom-made orthopedic implant, it is, in principle, essential to obtain image data using an appropriate image modality such as computed tomography (CT) or magnetic resonance imaging (MRI), and reconstruct geometrical data of the bone or the cartilage-containing joint of the patient, in order to make necessary geometrical modifications to a base ready-made product in a way that the implant matches the geometry of the bone or cartilage-containing joint of the individual patient. CT-based image extraction is the most common practice at present, but regardless of the modality used, the data reconstruction requires:

- Optimization of the imaging conditions, and
- Optimization of the image extraction and processing.

Presented below are general considerations.

1) Imaging and image construction conditions

In considering the balance between the exposure risk of the patient and the necessity of taking quality images adequate for the data reconstruction, imaging parameters listed below should be investigated to determine recommended conditions for them. The recommended conditions should be determined on the basis of relevant performance tests. If some parameters are

excluded from the determination, its justification should be presented. The date of taking images of the affected region should be specified.

A) For CT:

- Imaging equipment
- Voltage of X-ray tube
- Current of X-ray tube
- Scan slice thickness
- Beam pitch
- Scanning time
- Scan field of view (SFOV)
- Reconstruction slice thickness
- Reconstruction slice increment
- Reconstruction function
- Measures against artifacts

B) For MRI:

- Imaging equipment
- Coil
- Presence of absence of sequence fat suppression, and if present, its kind
- Scan section's echo time and repetition time (and if it exits, inversion time)
- Flip angle (for gradient echo)
- Scan slice thickness
- Field of view (FOV)
- Number of excitations
- Band width
- Sense factor or an analogous parameter
- Imaging time
- Reconstruction slice thickness
- Reconstruction slice increment
- Reconstruction direction
- Measures against artifacts

2) Image expiration

Although no specific restrictions exist for the timing of the 3D imaging, the images taken should not be used if the physician judges that the anatomical structure of the affected region may have changed, considering the characteristics of the concerned medical condition.

3) Effects of artifacts

If a foreign substance such as a metallic implant is seen in the image acquired, there may be concern that the substance might cause an increase in the CT level of the surrounding area, a filling defect, or another artifact, even if possible measures are taken at the time of imaging. The possibility that these artifacts

affect the precision of the reconstructed 3D model cannot be ruled out. If such image data need to be used, an appropriate action should be considered for it, such as evaluating the effect of the artifact with an appropriate method or stating clearly that the effect has not been evaluated and confirming that the physician determines that the geometry of the product meets the product specifications.

(2) Image Extraction and 3D Model Reconstruction

For the image extraction and 3D model reconstruction, the precision of the 3D model data should be clearly determined and presented.

Regardless of what kind of program is used to construct 3D model data from CT or other image data, the following points should be considered:

1) Handling of image data

If one intend to do image extraction and 3D model reconstruction on the request of a medical institution, one should establish appropriate measures to prevent leakage of personal information. (A consideration at the time of contract)

2) Method for extraction of 3D model data and determination of geometry

Requirements include:

- To enumerate the processes for the data extraction and the geometrical determination in detail and clearly indicate the responsible person for and the content of each process.
- To identify the program used to construct 3D model data.
- To evaluate the precision of the program again, if a modification of an algorithm or a change of the program itself that may affect the precision of the 3D model data occurs.
- To justify the method used for the 3D model segmentation (e.g., by explaining how to guarantee the skill of the operator, or for an automatic segmentation, by describing its precision and appropriateness).
- To show the precision of the process of the conversion to a geometrical shape. (Clarification of the condition required to guarantee the precision)

3) Acceptance criteria for the precision of the clinically needed 3D model data

Appropriate and adequate acceptance criteria for the precision of the 3D model data should be determined for each of the intended body regions to which the product is applied and for each of the intended purposes. The rationale for the criteria determined should be explained as scientifically as possible because it is expected that the performance desired for a medical device can vary depending on the body region.

(3) Design

Currently, some kinds of three-dimensional computer aided design (3D-CAD) programs have been used to design custom-made orthopedic implants. In

designing a custom-made orthopedic implant, the physician who requests the product is responsible for a significant part, but the MAH should also consider the following points:

1) Basic principle on the design

    (For example, that the design is achieved by customizing only the surface of the bone-implant interface using a basic design based on the base ready-made product's image data, or that the design is made as an optimized design achieved by making a customization after making a change(s) in an important functional part, e.g., the geometry of the sliding surface of a joint.)

2) When using the basic design approach, the manufacturing conditions based on the basic design used, how to evaluate the final product (the customized part) on the basis of relevant test results including those for mechanical safety and biological safety, the appropriateness of this evaluation method, and the method of validating the relevant conditions

3) When making a suitable design for each patient, what effects there are on the relevant factors such as the manufacturing conditions, mechanical safety, and biological safety as a result of the customization from a basic design, and how the non-inferiority to the basic design is evaluated

4) Conversion to manufacturing data
   - Method of converting data to the Standard Triangulated Language (STL) file format (Appropriateness of the method selection)
   - Presence or absence of geometry confirmation by means of visual inspection [Its necessity; if necessary, its method (e.g., superposition with a relevant CT image); and the appropriateness of the method]

(4) Examination of Final Geometry and Structure

To prove that custom-made orthopedic implants produced coincide with their design geometry within a certain error range, final products should be used to confirm the geometrical precision; the manufacturer should indicate the tolerance range and the appropriateness of the validation method for it in advance.

For the precision test, it is recommended to use a measuring method that allows three-dimensional measuring. For some products, one-dimensional measuring may be applicable depending on their shape, provided that its adequacy is shown. For surface roughness or a complex shape such as a porous structure, an appropriate method suitable for the structure should be used to individually test them, and therefore not only test results but the principle of the testing method, and the rationale and appropriateness of its use should be shown.

(5) Information That Should be Disclosed to Physician

The manufacturers of custom-made orthopedic implants are required to have established a procedure to disclose the following design-related information in response to a request from the physician who requested production of a custom-made implant. Additional disclosure may be required, as necessary.

1) The 3D image of the affected region and the final geometry of the designed custom-made orthopedic implant (for confirmation purpose)
2) The precision of the 3D image (errors and their possible causes: Bone density, cartilage, cartilage defect, etc.)
3) Details of image processing
4) The precision guaranteed for the designed and produced, final product or test results for it (e.g., cadaver study)
5) Recommended or tested imaging conditions