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Patient-Matched Guides to Orthopedic Implants

Draft Guidance for Industry and Food and Drug Administration Staff

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For questions about this document, contact the OPEQ: Office of Product Evaluation and Quality, OHT6: Office of Orthopedic Devices at (301) 796-5650.

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Preface

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DRAFT

Table of Contents

DRAFT

Patient-Matched Guides to Orthopedic Implants

Draft Guidance for Industry and Food and Drug Administration Staff

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I. Introduction

This draft guidance document provides recommendations regarding information that should be included in regulatory submissions for patient-matched guides to orthopedic implants. This document also provides recommendations that manufacturers should consider when developing their design process for these device types. Patient-matched guides are intended to assist in the execution of a pre-surgical plan concurred upon by the patient's healthcare professional to position an orthopedic implant in a way consistent with the implant's indicated use.

While this guidance includes considerations related to design aspects, it is not intended to comprehensively address all considerations or regulatory requirements to ensure your device is manufactured in accordance with quality system regulation requirements (21 CFR 820). For class II and class III devices such as identified in the scope of this guidance, manufacturers must establish and maintain procedures to control the design of the device to ensure that specified design requirements are met per 21 CFR 820.30, Design controls. Manufacturers must also establish and maintain procedures for monitoring and control of process parameters for validated processes to ensure that the specified requirements continue to be met.[1] Where the results of a process cannot be fully verified by subsequent inspection and testing, the process must be validated with a high degree of assurance and approved according to established procedures.[2] FDA interprets these regulations to require manufacturers to establish procedures including process validation of patient-matched guides to ensure that the device can perform as intended.

[1] 21 CFR 820.75(b).

[2] 21 CFR 820.75(a).

For the current edition of the FDA-recognized consensus standard(s) referenced in this document, see the FDA Recognized Consensus Standards Database.[3] For more information regarding use of consensus standards in regulatory submissions, please refer to the FDA guidance titled "Appropriate Use of Voluntary Consensus Standards in Premarket Submissions for Medical Devices."[4]

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

II. Background

Patient-matched guides[5] are designed to implement, in part or in whole, the pre-operative plan concurred upon by the patient's healthcare professional. The plan is based upon clearly identifiable landmarks on pre-operative patient images and within accordance to the implant system's indicated use.

As the designs of the patient-matched guides differ slightly between each patient, it is important to establish a design template and a range of pre-specified allowable design parameters to ensure a consistent and accurate guide. In general, the design process includes 1) patient image acquisition, 2) image quality control, segmentation, and anatomical definitions, 3) pre-operative planning and healthcare provider concurrence, 4) guide design and patient-matched features definition, and 5) guide construction. In addition to the design process, the preparation (cleaning/sterilization) and actual surgical use of the guide (surgical technique) are also critical to patient-matched guide performance.

III. Scope

The scope of this document is limited to patient-matched guides intended for use with legally marketed orthopedic implant systems that include recommended alignment parameters relative to rigid anatomical structures that can be identified on pre-operative imaging.

This guidance is intended to promote clarity and transparency as to expectations regarding submission recommendations for orthopedic patient-matched guides. Following such

[3] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm.

[4] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/appropriate-use-voluntary-consensus-standards-premarket-submissions-medical-devices.

[5] "Patient-matched guides" as discussed in this guidance are also commonly referred to as "patient-specific guides." These are distinct from "custom devices," as described in FDA's guidance entitled "Custom Device Exemption," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/custom-device-exemption.

recommendations may increase efficiency and consistency in review. Additionally, this guidance provides recommended best practices regarding certain elements of the design process.

IV. Submission and Design Recommendations

A. Indications for Use

The term "indications for use," as defined in 21 CFR 814.20(b)(3)(i), describes the disease or condition the device will diagnose, treat, prevent, cure or mitigate, including a description of the patient population for which the device is intended. To identify appropriate technical performance testing parameters, it is necessary to identify the indications for use of the patient-matched guide. For example, consistent with 21 CFR 801.6, the technical performance assessment for an orthopedic patient-matched guide that is indicated to support a specific implant system should evaluate the performance of the guide within that implant system's recommended surgical technique. Hence, it is important to consider any conflicts that may arise from the orthopedic patient-matched guide's indications for use and the implant system's cleared or approved indications/contraindications, which may translate into possible misbranding.[6] FDA considers the indications for use of an orthopedic patient-matched guide to include (but not be limited to) the following:

- The surgical approach and the procedure supported (e.g., total knee replacement, total hip replacement – Posterior-lateral surgical approach),
- The specific implant system(s) that the guide is intended to support,
- The patient population for which the guide is indicated and whether this is a subset of the implant system's indicated patient population, and
- The types of imaging modalities necessary for designing the guides (e.g., magnetic resonance imaging (MRI), computed tomography (CT)).
- The anatomic landmarks necessary for pre-operative planning that, at a minimum, should be clearly identified on the patient's pre-operative radiographic images.

B. Device Description

As the designs of the patient-matched guides differ slightly between each patient, it is important to establish and document the design process used to define a range of pre-specified allowable design parameters to ensure a consistent and accurate guide that correlates to the patient-matched guide's performance. As noted above, to ensure that specified design requirements are met per 21 CFR 820.30, manufacturers must establish and maintain procedures to control the design of the device. Therefore, the device description should encompass the patient-matched guide design as well as the design process and surgical use. This descriptive information is necessary to develop the appropriate technical performance testing parameters that are necessary to support a

[6] Per 21 CFR 801.6, "Among representations in the labeling of a device which render such device misbranded is a false or misleading representation with respect to another device or a drug or food or cosmetic." See also section 201(n) of the Federal Food, Drug, and Cosmetic Act.

DRAFT

regulatory submission. A complete device description should include (but not necessarily be limited to) the information outlined in each section below.

1. Patient-Matched Guide Description

Your submission should include the following information:

- A list of all guide components and available sizes, including information regarding the design envelope. If multiple guide designs are to be offered, a full description of each design should identify when each design is utilized. For example, if there are two different overall guide designs depending on surgical approach, an explanation of when each design is recommended should be provided.
- Fully dimensioned engineering drawings, including nominal dimensions with tolerances, of sample guides noting which critical-to-quality regions of the guides are fixed and which are variable based on patient anatomy. The drawings should also identify the limits associated with all variable dimensional aspects. For example, if the guide has a structural member that requires a minimum thickness to maintain structural integrity, this minimum thickness should be defined.
- A list of the specific implants that can be implanted using the guides, along with the implant system's 510(k), De Novo, or PMA number.
- A list of any ancillary components that may be included with the system. These components may include drop rods, pins, etc.
- A list of all accessories that are not included with the system, but are necessary to use the guide, listed with adequate specificity to allow for their acquisition by the end user. These accessories may include cut blocks, saw blades, etc.
- A list of all materials of construction (for both guides and provided accessories, if any) and method of manufacture.[7] This list should also include an identification of any color additives or coatings used.
- A description of the specific function of each guide design feature (e.g., hole for pin placement, slot for saw-blade guidance).
- A list of all software used with the device and a description of the specific function of the software (e.g., pre-surgical planning, image segmentation, guide design). Please see Section IV.C. for additional software recommendations.

[7] If you intend to use additive manufacturing methods for your device, please see FDA's guidance entitled "Technical Considerations for Additive Manufactured Medical Devices," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/technical-considerations-additive-manufactured-medical-devices.

DRAFT

2. General Design Process Description

To assist in the characterization of the device and its performance, your submission should include the following information:

- A description of the overall process, such as a flowchart, that details the involved parties and the steps involved in designing and creating the guides. This should include an explanation of how such processes will be utilized to match the patient anatomy with adequate fit and fidelity to achieve the intended effect.

In designing and developing your guide, you should consider the following:

- Establishing a mechanism to ensure that the patient's pre-operative plan is maintained throughout the guide's design and manufacturing process. For example, you should develop a method for patient case identification (e.g., marking with UDI or other patient identification method) on the guide itself.
- Identifying any qualifications and training pertaining to the end user and persons involved in the design process.
- Developing a process to ensure that compatibility of the patient-matched guide will be monitored and maintained for the indicated implants, including from third party manufacturers . Establishing an agreement with such a third party implant manufacturer to communicate implantation or dimensional modifications would be one method to accomplish this.

3. Patient Image Acquisition Description

To identify appropriate performance testing considerations, your submission should include a summary of an imaging protocol(s) for obtaining the patient pre-operative images that are used for guide design. Please note that the minimum imaging specifications from this protocol should be considered when identifying worst-case technical performance testing (see Section IV.G.). Your imaging protocol should be developed considering the image modality's accuracy and limitations, the parameters necessary for surgical planning and guide design, the surgical procedure, the presence of deformity that may impact subject device performance, patient disease level (e.g., large defects), and any additional hardware that may already exist in the anatomical location. These factors can affect image acquisition and mitigation measures should be adequately described.

4. Image Quality Control, Segmentation, and Anatomical Definitions Description

To ensure reproducibility of performance testing results, your submission should include the following information:

DRAFT

- A summary description of your image processing methods to illustrate how the patient image(s) is received and manipulated prior to pre-operative planning.
- A description of any software used for manual or automatic segmentation. If automation is utilized, appropriate software verification/validation should be provided to support regulatory evaluation. For automated segmentation processes, the same datasets should not be used for verification/validation as was used for software development.
- The necessary anatomical landmarks for designing the guide. The necessary anatomical landmarks should be clearly defined to allow for reproducible identification and transparency to the end user.
- A description of any software algorithms that are used to automate the definition of anatomic landmarks, axes, and planes and quality control measures associated with this process. For automated anatomical landmark identification, the same datasets should not be used for verification/validation as was used for software development.

For more information on software recommendations for these devices, please see Section IV.C.

In developing your patient image processing methods, you should consider the following:

- Establishing a patient image quality check, including critical parameter checks and an identification of the responsible party. The patient image quality check should clearly identify how incoming images are analyzed for compliance with the radiographic protocol(s).
- Developing a segmentation protocol(s) for processing the patient images. The segmentation protocol should clearly instruct the responsible persons on how to address abnormalities within segmented volumes and identify any conditions that may prevent development of an adequate patient model.

5. Pre-operative Planning and Healthcare Professional Concurrence Description

To develop instructions for use allowing for the device to be used safely and for the purpose for which it is intended,[8] your submission should include the following information:

- Implant planning and alignment methods and goals. The planning process description should identify implant alignment methods and goals consistent with those specified by the implant manufacturer for each implant system with which the guide is intended to be compatible.
- A description of the healthcare professional's involvement in the guide design process, including an identification of the parameters that can be modified, and at which steps the healthcare professional provides input and concurrence. If the healthcare professional has access to pre-operative planning images and/or software, the quality and resolution of these images should be described to the healthcare professional within the images and/or

[8] 21 CFR 801.109(c).

software. When the original patient image quality or resolution is altered by the manufacturer, we recommend that the manufacturer indicate within the image(s) and/or software that the image(s) are intended for pre-operative planning only and are not intended for diagnostic purposes.

- A description of how requests for plan (e.g., surgical, guide design) modifications and the final plan concurrence are processed and documented by the guide manufacturer and the healthcare professional.
- An example of any surgical proposal(s) or final report(s) that are communicated to the healthcare professional. These proposals/reports should include adequate information and image definition to inform the healthcare professional of the proposed surgical plan to ensure knowledgeable concurrence.

6. Guide Design and Patient-Matched Features Definition Description

To assist in the characterization of the device and its performance, your submission should include the following information:

- A summary description of the guide design process to illustrate how the generic guide model is modified to yield a patient-matched guide, including the targeted bone/guide interface location. The description should also identify how the resulting guide features (e.g., pin location, cut slot location) correlate with the implant system's alignment recommendations.

In developing your guide design and patient-matched feature definitions methods, you should consider the following:

- Establishing a process for modifying generic guide models to allow for patient specific features. The process should identify critical structures, such as cut slots, drill guides, etc., whose positioning is crucial for proper guide function. The process should also specify how these structures are positioned and controlled throughout the design process.
- Identifying default values with upper and lower limits for each planning parameter (e.g., pin location, resection angle, implant position).

7. Guide Construction Description

In developing your guide construction methods, you should consider the following:

- Determining how, during the manufacturing process, quality control in regard to the dimensional characteristics is maintained for the manufactured guide.[9] You should

[9] For specific considerations regarding additively-manufactured devices, please see FDA's guidance document entitled "Technical Considerations for Additive Manufactured Medical Devices," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/technical-considerations-additive-manufactured-medical-devices

identify pre-determined dimensional specifications and tolerances for accepting the final guide such that the technical performance testing can be considered representative of the predefined manufacturing tolerances.

8. Surgical Technique Description

To develop instructions for use allowing for the device to be used safely and for the purpose for which it is intended,[10] your submission should include the following information:

- A description of how the guide's recommended surgical technique is compatible with the implantation technique recommended by the implant manufacturer.
- A description of any methods available for converting to traditional manual implantation techniques (if appropriate) and at which surgical steps this conversion is possible.
- A description of how the healthcare professional would detect and remedy an incorrect guide alignment or surgical outcome.
- A description of any additional considerations that may be necessary due to anatomical variation in the indicated patient population (e.g., patient size, bone condition).

C. Software

Significance: Software used in the development of patient-matched guides may use proprietary and/or off-the-shelf software to support pre-operative planning and guide design. This software ensures that a pre-operative plan is developed and correctly implemented within the guide design parameters. Adequate software performance testing provides assurance that the software operates as intended to ensure accurate and reproducible results for the compatible implant system(s).

Recommendation: As a reference for developing, performing, and documenting software performance testing, refer to the FDA software guidance, "Content of Premarket Submissions for Device Software Functions"[11] for a discussion of the software documentation that you should provide in your submission.

To assess the adequacy of your performance testing, we recommend that you provide a full description of the software/firmware supporting pre-operative planning and guide design following the software guidance, commensurate with the appropriate Documentation Level as described in the guidance. This recommendation applies to original device/systems as well as to any software/firmware changes made to already-marketed systems. Changes to software must be revalidated and reverified in accordance with Design Controls, 21 CFR 820.30(g)(i), and documented in the Design History File, 21 CFR 820.30(j). Some software changes may warrant the submission of a new marketing submission. For additional information regarding software modifications, please see FDA guidances "Deciding When to Submit a 510(k) for a Software

[10] 21 CFR 801.109(c).

[11] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/content-premarket-submissions-device-software-functions.

Change to an Existing Device" and "Modification to Devices Subject to Premarket Approval (PMA) – The PMA Supplement Decision-Making Process."[12]

The design process may use third-party software to aid in guide design. If the device includes off-the-shelf software, you should provide the additional information as recommended in the FDA documents titled "Off-the-Shelf Software Use in Medical Devices"[13] and "Cybersecurity for Networked Medical Devices Containing Off-The-Shelf (OTS) Software."[14]

As appropriate, you should also provide information on the Cybersecurity aspects of your device. For more information on this topic, please see FDA's guidance "Content of Premarket Submissions for Management of Cybersecurity in Medical Devices."[15]

Overall, the documentation related to the software should provide sufficient evidence to describe the role of the software used to develop the device, and functions to produce a guide that performs as intended.

D. Biocompatibility

Significance: Patient-matched guides contain patient-contacting materials, which, when used for their intended purpose, i.e., contact type and duration, may induce a harmful biological response.

Recommendation: You should determine the biocompatibility of all patient-contacting materials present in your device. If your device is identical in composition and processing methods to patient-matched guides with a history of successful use, you can reference previous testing experience or the literature, if appropriate. For some device materials, it may be appropriate to reference to either a recognized consensus standard, or to a Letter of Authorization (LOA) for a device Master File (MAF). You should refer to the following FDA webpage for additional information on using device MAFs: https://www.fda.gov/medical-devices/premarket-approval-pma/master-files.

If you are unable to identify a legally marketed device with similar location/duration of contact and intended use that uses the same materials and processing methods as used in your device, we recommend you conduct and provide a biocompatibility risk assessment. The assessment should explain the relationship between the identified biocompatibility risks, the information available to mitigate the identified risks, and any knowledge gaps that remain. You should then identify any biocompatibility testing or other evaluations that were conducted to mitigate any remaining risks.

[12] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/deciding-when-submit-510k-software-change-existing-device and https://www.fda.gov/regulatory-information/search-fda-guidance-documents/modifications-devices-subject-premarket-approval-pma-pma-supplement-decision-making-process.
[13] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/shelf-software-use-medical-devices.
[14] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cybersecurity-networked-medical-devices-containing-shelf-ots-software.
[15] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/content-premarket-submissions-management-cybersecurity-medical-devices.

We recommend that you follow FDA's guidance "Use of International Standard ISO 10993-1, 'Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process,'" [16] which identifies the types of biocompatibility assessments that should be considered and recommendations regarding how to conduct related tests.

Per ISO 10993-1: *Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process* and Attachment A of FDA's guidance on ISO-10993-1, patient-matched guides are external-communicating devices in contact with tissue/bone/blood for a limited contact duration. Therefore, the following endpoints should be addressed in your biocompatibility evaluation:

- cytotoxicity;
- sensitization;
- irritation or intracutaneous reactivity;
- acute systemic toxicity;
- material-mediated pyrogenicity.

As patient-matched guides often utilize additive manufacturing techniques, it is important to consider the impact of the manufacturing process on the biocompatibility of the patient-contacting materials. Additive manufacturing should utilize quality controls to ensure that foreign material or re-used material does not influence guide biocompatibility. Refer to the FDA guidance, "Technical Considerations for Additive Manufactured Medical Devices," [17] for additional information regarding the possible impact of additive manufacturing on material biocompatibility.

E. Sterility

Significance: Patient-matched guides come in contact with blood and bone and should be adequately sterilized to minimize infections and related complications. They are either provided sterile to the user or are single-use end-user sterilized devices.

1. Devices provided sterile

Recommendation: For patient-matched guides labeled as sterile, we recommend that you develop information outlined below:

1. For the sterilization method:
   a. a comprehensive description of the sterilization method/process;
   b. a description of the sterilization chamber if not rigid, fixed (e.g., flexible bag);

[16] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-international-standard-iso-10993-1-biological-evaluation-medical-devices-part-1-evaluation-and.

[17] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/technical-considerations-additive-manufactured-medical-devices-guidance-industry-and-food-and-drug.

DRAFT

c. the sterilization site;
d. in the case of radiation sterilization, the radiation dose;
e. for chemical sterilants (e.g., EO, H_2O_2), the maximum levels of sterilant residuals that remain on the device, and an explanation of why those levels are acceptable for the device type and the expected duration of patient contact.

   In the case of EO sterilization, CDRH has accepted EO residuals information based on the currently recognized version of the standard, "AAMI/ANSI/ISO 10993-7: *Biological Evaluation of Medical Devices – Part 7: Ethylene Oxide Sterilization Residuals*."

2. For the sterilization method, a description of the method used to validate the sterilization cycle as well as the sterilization validation data.[18] A premarket submission should also identify all relevant consensus standards[19] used and identify any aspects of the standards that were not met. In the absence of a recognized standard, a comprehensive description of the process and the complete validation protocol should be submitted and reviewed.

3. You should state the sterility assurance level (SAL) of 10^{-6} for devices labeled as sterile unless the device is intended only for contact with intact skin.

As patient-matched guides rely upon a specific geometrical configuration to establish a unique alignment to the patient's anatomy, it is important to consider the impact of the sterilization process on the guide's geometrical configuration. During development of the sterilization process, manufacturers should ensure that guides do not deform unacceptably during the final recommended sterilization process.

2. Single-use devices provided non-sterile and intended for sterile processing

Recommendation: Instructions on how to reprocess a single-use device that is provided non-sterile to the user are critical to ensure that a device is appropriately prepared for its use. For recommendations regarding the development and validation of reprocessing instructions, refer to the guidance "Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling."[20]

[18] Submission of validation protocols and data is only recommended for certain premarket submission types and sterilization methods. For additional information regarding submission recommendations for sterility information in 510(k)s, please see Submission and Review of Sterility Information in Premarket Notification (510(k)) Submissions for Devices Labeled as Sterile, available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/submission-and-review-sterility-information-premarket-notification-510k-submissions-devices-labeled.

[19] Please refer to FDA's recognized standards database FDA Recognized Consensus Standards Database, available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm for applicable consensus standards depending on the type of sterilization method chosen for your device.

[20] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/reprocessing-medical-devices-health-care-settings-validation-methods-and-labeling.

As patient-matched guides rely upon a specific geometrical configuration to establish a unique alignment to the patient's anatomy, it is important to consider the impact of the cleaning and sterilization process on the guide's geometrical configuration. During development of the cleaning and sterilization processes, manufacturers should ensure that guides do not deform unacceptably during the final recommended cleaning and sterilization processes.

F. Shelf Life and Packaging

Significance: If the patient-matched guide is provided non-sterile, shelf life should reflect an appropriate duration between the acquisition of patient imaging and the planned surgical intervention to ensure that the anatomical situation has not changed such that guide performance can be affected. If the patient-matched guide is provided sterile, shelf life testing should additionally be conducted to support the proposed expiration date through evaluation of the package integrity for maintaining device sterility and/or evaluation of any changes to device performance or functionality.

Recommendation: With respect to package integrity for maintaining device sterility, you should develop a description of the packaging, including how it will maintain the device's sterility. You should also maintain the protocol(s) used for your package integrity testing, the results of the testing, and the conclusions drawn from your results. We recommend that a package validation study include simulated distribution and associated package integrity testing, as well as an aging process (accelerated and/or real-time) and associated seal strength testing, to validate package integrity and shelf life claims. We recommend you follow the methods described in the FDA-recognized series of consensus standards ANSI/AAMI/ISO 11607-1: *Packaging for terminally sterilized medical devices – Part 1: Requirements for materials, sterile barrier systems and packaging* and ANSI/AAMI/ISO 11607-2: *Packaging for terminally sterilized medical devices – Part 2: Validation requirements for forming, sealing and assembly processes*.

We recommend devices undergo real-time aging to determine the effects of aging on the maintenance of sterility. If you use devices subjected to accelerated aging, we recommend that you specify the way in which the device was aged and develop a rationale to explain how the results of shelf life testing based on accelerated aging are representative of the results if the device were aged in real time. We recommend that you age your devices as per the currently FDA-recognized version of ASTM F1980: *Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices* and specify the environmental parameters established to attain the expiration date. Testing of real-time aged devices can be conducted in parallel with submission review, with results documented to file in the design history file (i.e., complete test reports do not need to be submitted to FDA).

With respect to patient-matched guides provided non-sterile, the maximum time between the acquisition of patient's images and planned surgical intervention should be specified. The shelf life should be based upon the indicated patient pathology and sensitivity of the patient-matched regions to continued disease progression. The shelf life for guides provided sterile should not exceed the duration for which the anatomical situation may change.

DRAFT

As patient-matched guides rely upon a specific geometrical configuration to establish a unique alignment onto the patient's anatomy, we also recommend that guide deformation as a result of shipping be considered. Additional dimensional testing should demonstrate that guides do not deform following simulated distribution testing. For additional information, please see Section IV.G.2.

G. Non-Clinical Performance Testing

For information on recommended content and format of test reports for non-clinical bench performance testing described in this section, refer to FDA's final guidance, "Recommended Content and Format of Non-Clinical Bench Performance Testing Information in Premarket Submissions."[21]

1. Intra- and Inter-Designer Variability

Significance: The patient-matched guide design process should yield reproducible results for patient data sets within individual designers and across multiple designers. High designer variability may cause patient-matched guides to misalign implants. Variability testing provides assurance that the design process reliably outputs adequate specifications to yield reproducible clinical results.

Recommendation: We recommend that you investigate intra- and inter-designer variability across representative patient data sets and designers. Variability in segmentation, patient modeling, anatomical landmark definition, preoperative planning, and guide creation should be addressed by your testing. We recommend you utilize established work instructions to evaluate the ability of multiple designers to follow the provided instructions. We recommend that the selected data sets represent the anticipated patient population, and that the selected designers represent different experience levels with the work instructions. We recommend that any observed variability be analyzed regarding the impact on the planned implant position.

2. Mechanical Integrity (Post-Processing)

Significance: Patient-matched guides rely upon geometrical specifications to align implants to the patient's anatomy. Shipment, processing (e.g., cleaning and sterilization), and clinical use in the surgical environment can cause patient-matched guides to mechanically distort or fail, potentially yielding inaccurate implant alignment. Mechanical analysis following shipping, processing, and anticipated clinical loading provides assurance that the guide design is of sufficient strength and functions effectively.

Recommendation: We recommend that you conduct dimensional and mechanical evaluations to assess that guide stability and strength is adequate to withstand forces associated with worst-case

[21] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/recommended-content-and-format-non-clinical-bench-performance-testing-information-premarket.

conditions relative to transit, cleaning/sterilization, and use in the surgical environment. If you label your device for cleaning/sterilization and use after an accidental impact (dropping), we recommend drop testing to validate dimensional stability and validation of additional sterilization cycles. Justification should be documented for the selected worst-case conditions including the selected worst-case guide design.

3. Debris Generation

Significance: Interaction between polymeric patient-matched guides and the specified surgical instruments can generate debris that can be implanted. The generated debris can cause biocompatibility and/or mechanical concerns to the patient and/or implant system. Debris generation testing quantifies the magnitude and type of debris that may be generated during use.

Recommendation: We recommend that you conduct simulated use testing utilizing the specified surgical instruments under worst-case contact conditions to measure the amount, size and shape of debris generated per ASTM F1877: *Standard Practice for Characterization of Particles*. The biocompatibility ramifications of the generated debris should be evaluated. We recommend the magnitude and size of debris generated should be less than or equal to a similar, legally marketed device with the same intended use, or should meet or exceed clinically justified acceptance criteria.

4. Implant Alignment Accuracy and Guide Usability

Significance: Patient-matched guides are intended for aligning orthopedic implants relative to anatomical landmarks identified on pre-operative images as recommended by the orthopedic implant manufacturer. Implant misalignment can cause premature implant failure and impact patient outcomes.

Recommendation: We recommend that you conduct objective, clinically relevant evaluations to assess the usability and accuracy with which the patient-matched guides recreate the pre-surgical plan.

While benchtop evaluations may be useful in early verification activities, validation of the system performance including bone and soft tissue interaction should be performed in a cadaveric model to test the "fit," feasibility, and accuracy of the guide within the surgical workflow. Soft tissue interaction is also critical in establishing the feasibility in preparing the surgical site when removal of cartilage and/or osteophytes is appropriate.

We recommend cadaveric testing of the worst-case guide configuration by multiple independent healthcare professionals with varied experience (3 levels: novice, intermediate, expert) in the surgeries associated with anatomical location using patient-matched guides, with a statistically and/or clinically supported sample size for each general guide design and for each proposed surgical technique. (Note that additional samples may be requested if error variability is large or if other unanticipated observations occur.) A worst-case scenario justification should be provided. The justification should consider various parameters such as guide configuration,

DRAFT

cleaning, sterilization, guide fit, anatomical positioning, surgical approach, implantation technique, pathological conditions for the intended patient population, and cadaveric anatomical conditions. We also recommend that these activities document the usability of the guide within the implant surgical technique(s) and assess the guide's unique and stable fit to the anatomy.

The final implant alignment and/or bone preparation should be quantitatively compared to the pre-surgical plan. Descriptive statistics (including mean absolute error, standard deviation, and maximum error of the measured parameters) should be provided and demonstrated to be less than or equal to a legally marketed device with the same intended use and/or clinically justified acceptance criteria. If justifying acceptance criteria with a clinical rationale, the acceptance criteria should be established to include consideration for the sensitivity of the surrounding anatomy and impact on implant performance due to malalignment. Clinically justified acceptance criteria should not exceed that applied to a legally marketed device with the same intended use (if available), unless an equivalent benefit-risk profile is demonstrated. An analysis of performance testing results should be conducted to describe the expected clinical accuracy. The complete data set may be requested to perform further analysis. In addition, a healthcare professional should document any observations and indicate that the prosthesis can be implanted using the guides to their satisfaction.

H. Clinical Performance Testing

Clinical performance testing is generally not necessary to support regulatory evaluation of orthopedic patient-matched guides. However, clinical performance testing may be requested to address certain situations that cannot be adequately addressed through bench testing alone, such as:

- indications for use dissimilar from legally marketed devices of the same type;
- significantly different technological characteristics;
- cases where engineering and/or cadaveric testing raise issues that warrant further evaluation with clinical evidence;
- labeling claims about improved patient outcomes or reduced surgical time; and/or
- a surgical approach, implant alignment specifications, or indications for use other than that recommended by the implant manufacturer.

We will consider alternatives to clinical testing when the proposed alternatives are supported by an adequate scientific rationale. If a clinical study is needed to support marketing authorization, the study must be conducted under the Investigational Device Exemptions (IDE) regulation, 21 CFR 812. Generally, we believe patient-matched guides addressed by this guidance document are significant risk devices subject to the requirements in 21 CFR 812. See the FDA Guidance titled, "Significant Risk and Nonsignificant Risk Medical Device Studies."[22] In addition to the requirements in 21 CFR 812, sponsors of such trials must comply with the regulations governing institutional review boards (21 CFR 56) and informed consent (21 CFR 50).

[22] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/significant-risk-and-nonsignificant-risk-medical-device-studies.

In some cases, "real-world data" (RWD) may be used in lieu of traditionally-collected clinical data. Whether the collection of RWD for a legally marketed device requires an IDE depends on the particular facts of the situation. Specifically, if a device is being used in the normal course of medical practice, an IDE would likely not be required. For additional information regarding this topic, please refer to the FDA Guidance entitled "Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices." [23]

I. Labeling

As prescription devices, patient-matched guides are exempt from having adequate directions for lay use required under section 502(f)(1) of the Federal Food, Drug and Cosmetic Act as long as the conditions in 21 CFR 801.109 are met. For instance, labeling must include adequate information for the intended user of the device, including indications, effects, routes, methods, frequency and duration of administration and any relevant hazards, contraindications, side effects, and precautions (21 CFR 801.109(d)).

The inclusion of the following additional information unique to this device type is also recommended:

- information regarding the implant systems for which the device has been designed and tested to be compatible;
- instructions regarding how the user should assess proper guide alignment;
- instructions regarding conversion to a traditional implantation technique if the user is unable or unwilling to use the patient-matched guides;
- instructions to irrigate the region during situations where polymeric debris is being generated;
- graphical illustrations of key steps that may otherwise be unclear; and
- a description of the convention used to ensure that the user can map the pre-operative plan to the final guide.
- a means of identifying the patient for which the guide was created. This identification is recommended to reduce the potential for using a guide on an incorrect patient and should be placed directly on the guide (for example, by marking with UDI or other patient identification method).

J. Modifications (Devices subject to 510(k))

In accordance with 21 CFR 807.81(a)(3), a device change or modification "that could significantly affect the safety or effectiveness of the device" or represents "a major change or

[23] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-real-world-evidence-support-regulatory-decision-making-medical-devices.

DRAFT

614 modification in the intended use of the device" requires a new 510(k).[24] The changes or
615 modifications listed below are examples of changes that may require submission of a new
616 510(k). Note that this list is not exhaustive but provides examples of modifications that are likely
617 to require submission of a new 510(k). For additional details, please see FDA guidances
618 *"*Deciding When to Submit a 510(k) for a Change to an Existing Device"[25] and *"*Deciding When
619 to Submit a 510(k) for a Software Change to an Existing Device."[26]
620
621 Such changes or modifications include:
622
623 • **Design of the patient contacting regions, guiding slots/holes, or critical guide**
624 **structure.** FDA considers the modification to the design of the patient contacting regions
625 of the guide to be a significant change, which could significantly affect the use of the
626 device, including both safety and effectiveness, by impacting final device alignment,
627 resulting bone preparation, and guide integrity.
628 • **Planning process - automate a manual segmentation step.** A modification in the
629 planning process such as automating a manual segmentation step may be a significant
630 change which could significantly affect both safety and effectiveness of the device by
631 producing an inaccurate patient-matched guide that does not correspond to the patient's
632 anatomy due to an error in the segmentation process, which could lead to implant
633 malalignment.
634 • **Patient imaging modality.** FDA considers a modification in the patient imaging
635 modality such as changing from MRI to CT to be a significant design change, which
636 could significantly affect both safety and effectiveness of the device by impacting final
637 device alignment due to an inaccurate patient-matched guide that does not reflect the
638 limitations of the new imaging modality.
639 • **Anatomic contact location.** Modifications to the anatomic contact location for a patient-
640 matched guide may pose significant changes to the guide's stability and fit which could

[24] Section 3308 of the Food and Drug Omnibus Reform Act of 2022, Title III of Division FF of the Consolidated Appropriations Act, 2023, Pub. L. No. 117-328 ("FDORA"), enacted on December 29, 2022, added section 515C "Predetermined Change Control Plans for Devices" to the FD&C Act (section 515C). Under section 515C, FDA can approve or clear a predetermined change control plan (PCCP) for a device that describes planned changes that may be made to the device and that would otherwise require a supplemental premarket approval application or premarket notification. For example, section 515C provides that a supplemental premarket approval application (section 515C(a)) or a premarket notification (section 515C(b)) is not required for a change to a device if the change is consistent with a PCCP that is approved or cleared by FDA. Section 515C also provides that FDA may require that a PCCP include labeling for safe and effective use of a device as such device changes pursuant to such plan, notification requirements if the device does not function as intended pursuant to such plan, and performance requirements for changes made under the plan. If you are interested in proposing a PCCP in your marketing submission, we encourage you to submit a Pre-Submission to engage in further discussion with CDRH. See FDA's guidance "Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/requests-feedback-and-meetings-medical-device-submissions-q-submission-program.

[25] https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm514771.pdf https://www.fda.gov/regulatory-information/search-fda-guidance-documents/deciding-when-submit-510k-change-existing-device.

[26] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/deciding-when-submit-510k-software-change-existing-device.

DRAFT

significantly affect safety and effectiveness by misaligning the implant compared to the pre-operative planning.

FDA believes that the following modifications would likely not require submission of a new 510(k):

- **Software update to off-the-shelf segmentation software.** This modification does not introduce new risks that would significantly affect safety or effectiveness.
- **Format of the Pre-operative Planning Report.** Modifications to improve usability of the pre-operative planning report that do not alter the informational content.
- **Non-patient contacting and non-critical guide structure.** Modifications to the non-patient contacting and non-critical guide structures to increase intra-operative usability that do not impact upon the guide's structural integrity (i.e., rounding an external edge, placing an external divot to indicate recommended user finger placement during alignment) would likely not require submission of a new 510(k).

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