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ALERTS

FDA Issues Final Guidance On Technical Considerations For Additive Manufactured Devices, Including 3-D Printing

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Among several guidance documents released last month, the Food and Drug Administration (FDA) issued a final guidance for medical device manufacturers titled "Technical Considerations for Additive Manufactured [AM] Devices," which covers 3-D printing, among other things. The guidance "outline[s] technical considerations associated with AM processes, and recommendations for testing and characterization for devices that include at least one AM fabrication step." The guidance also includes recommendations on information to include in applications for marketing clearance or approval. This alert includes many of the recommendations in the guidance and omits many of the accompanying explanations. The explanations generally relate to challenges the AM process poses to producing quality devices consistently.

Design and Manufacturing Considerations

The first section discusses technical considerations in design and manufacturing considerations that manufacturers should address "as part of fulfilling quality system (QS) requirements for their devices, as determined by the regulatory classification of the device or the regulation to which the device is subject, if applicable."

A. Device Design

1. Standard-Sized Device Design

The guidance notes that AM introduces variability into the design process that may not be present when using other manufacturing techniques and thus recommends that firms compare the minimum possible feature size of their AM technique, in addition to the manufacturing tolerances of the machine, to the desired feature sizes of their final finished device. "Dimensional specifications for the final device or component, as well as manufacturing tolerances of the machine, should be documented." Any pixelation of features caused by mismatch of machine resolution and model resolution should be identified.

2. Patient-Matched Device Design

Some devices can be matched to a patient's anatomy. The considerations for standard devices also apply to matched devices. For such non-standard devices, the FDA recommends that manufacturers clearly identify clinically relevant design parameters, the range

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(minimum/maximum) for these parameters, and which of these parameters can be modified for patient-matching.

Further, the guidance recommends that manufacturers of patient-matched devices consider the several factors where applicable. Two of these, complex design files and cybersecurity/personally identifiable information, appear in the final guidance, but did not appear in the draft version.

a. Effects of imaging

The guidance states that manufacturers should take into account several factors that may affect the fit of AM devices that use patient imaging to precisely control their size or shape, including, but not limited to:

- the minimum image feature quality and resolution used for matching,
- any smoothing or image-processing algorithms that may alter the dimensions of the final device when compared to the reference,
- anatomy,
- the rigidity of the anatomic structures being imaged, and
- the clarity of anatomic landmarks used to match the device to the patient's anatomy.

Because a patient's anatomy can change over time (e.g., with disease progression), the time that can elapse between when the patient is imaged and when the final device is used should be reflected in the expiration date of the device.

b. Interacting with design models

The final guidance recommends that any software or procedure used to make modifications to the device design based on clinical input should include internal checks that prevent the user from exceeding the pre-established device specifications documented in the device master record. The design manipulation software should identify the iteration of the design to which the user is making changes. Firms should also identify all medical devices and accessories with which the design manipulation software is validated to work.

c. Complex design files

The guidance notes that "patient-matched devices that follow the patient anatomy precisely are especially vulnerable to errors in file conversion because anatomic curves are typically geometrically or mathematically complex." Accordingly, the FDA recommends following the considerations on maintaining data integrity throughout the conversion process, which are set out in a later section of the final guidance.

d. Cybersecurity and personally identifiable information

Noting that these issues are beyond the scope of this guidance, the FDA includes links to the HHS “Guidance on Significant Aspects of the Privacy Rule” and, for device designers who include interactive steps in their patient matching workflow, to the FDA’s guidance on the “Content of Premarket Submissions for Management of Cybersecurity in Medical Devices.”

B. Software Workflow

1. File format conversions

The guidance notes that AM can involve interaction between several different software programs and cautions “[e]rrors in file conversion can negatively impact final finished device and component properties, such as dimensions and geometry.” Thus, the FDA recommends that firms “test all file conversion steps with simulated worst-case scenarios to ensure expected performance, especially for patient-matched devices.”

2. Digital device design to physical device

According to the final guidance, the process of converting a digital device design to a physical device can be divided into four steps: 1) build volume placement, 2) addition of support material, 3) slicing, and 4) creating build paths.

a. Build volume placement

Placement and orientation of devices or components within the build volume is integral to individual device or component quality.

b. Addition of support material

Because of the layer-by-layer printing process, some types of AM require temporary support structures for certain design features during printing. The location, type, and number of supports can affect the geometric accuracy and mechanical properties of the final finished device or component.

c. Slicing

Because the thickness of the slices of the layers in an AM device can have several effects that relate to device quality, the FDA states that the choice of layer thickness should be documented and reflect a balance among the above-mentioned effects, accuracy, quality, and printing speed.

d. Creating build paths

The build path, or the path traced by the energy or material delivery system, can impact the quality of the final finished device or component. Thus, maintaining the consistency of the build path between identical devices and components is important. If more than one build path is used,

the firm should document each build path. The FDA also recommends that firms assess whether differences in the build path significantly affect the performance of each component or device.

e. Machine parameters and environmental conditions

To make quality AM devices, firms must maintain proper calibration and perform preventative maintenance on the AM machines. Environmental conditions within the build volume can also affect part quality, so firms must establish and maintain procedures to adequately control environmental conditions.

C. Material Controls

1. Starting materials

Because the starting material can significantly impact the quality of the finished device, the guidance recommends that firms document the following information:

- identity of the material or chemical by common name, chemical name, trade names and Chemical Abstracts Service (CAS) number,
- material supplier, and
- incoming material specifications and material certificates of analysis (COAs), with the test methods used for the COAs.

2. Material reuse

For firms that recycle starting material, the guidance recommends that firms describe the material recycling process, including a description of recycling processes such as filtering recycled material, or monitoring for changes in chemistry, oxygen, or water content. The FDA also recommends that firms document evidence that material recycling does not adversely affect the final device.

D. Post-processing

Post-processing steps range from cleaning away excess starting material, through annealing the device to relieve residual stress, to final machining. The guidance states that firms document all post-processing steps and include a discussion of the effects of post-processing on the materials used and the final device. The FDA also recommends that firms identify any potentially detrimental effects of post-processing and describe mitigations implemented.

E. Process Validation and Acceptance Activities

1. Validation

In contrast to the many recommendations discussed above, the guidance states that process validation must be performed to ensure and maintain quality for all devices and components built in a single build cycle,

between build cycles, and between machines, where the results of a process (i.e., output specifications) cannot be fully verified by subsequent inspection and test. Software also must be validated for its intended use according to an established protocol (i.e., software workflow).

2. Revalidation

Changes to the manufacturing process or process deviations can trigger the need for revalidation, and firms should identify these changes or deviations for each process.

3. Acceptance activities

Some acceptance activities for individual devices or components can be performed through non-destructive evaluation (NDE). Specifically, NDE techniques can be used for the verification of geometry, microstructure, and some performance characteristics. The final guidance refers to protocols developed by the ASTM Committee on Additive Manufacturing Technologies.

4. Test coupons

A “test coupon” is a representative test sample of the device or component. The FDA recommends that coupons be used for process validation, and to identify worst-case conditions in the manufacturing process (e.g., worst-case orientation and location in build volume). Firms can also use test coupons for in-process monitoring by placing them in build volume locations that are known to have the worst-case outputs.

Compared to the draft version, the final guidance clarifies that test coupons may not be necessary if the manufacturing process is validated per QSR requirements and test coupons are not a process monitoring activity defined in the manufacturer’s quality system.

F. Quality Data

Firms should ensure that quality data such as build volume location can be analyzed to enable proper identification of quality problems and investigation of the cause of nonconformities.

Device Testing Considerations

The second section contains a description of the type of information that the FDA recommends firms include in a premarket submission of a device made using AM.

A. Device Description

The guidance states that firms should document the range of dimensions for the device, any design variations, critical dimensions or feature to match a patient, a range of allowable values for such parameters, and the type of AM technology used. Applications should include a flow chart describing the AM process, including post- processing, in order to help the FDA determine if additional assessments are needed. The FDA recommends that critical features of the device be clearly described in the device description and identified in technical drawings.

B. Mechanical Testing

The type of performance testing that should be conducted on a device made using AM is generally the same as that for a device manufactured using a traditional manufacturing method. Performance testing should be conducted on final finished devices subjected to all post-processing, cleaning, and sterilization steps. Since mechanical properties of the device may be impacted by orientation and location, firms must ensure that production processes are properly developed, conducted, controlled, and monitored to ensure devices or components are not adversely affected by fabrication orientation.

C. Dimensional Measurements

The guidance states that device dimensions can also be affected by orientation and location within the build space, so it recommends that firms specify the dimensional tolerances and perform dimensional measurements for each additively manufactured component. To demonstrate consistency and reproducibility between build cycles, manufacturers should make dimensional measurements on samples from multiple build cycles, and provide a justification on the sampling scheme used. Alternatively, firms may use process validation information to demonstrate that there is negligible variability between build cycles.

D. Material Characterization

1. Material chemistry

All materials involved in the manufacturing of the device should be identified, including the source and purity of each material used. Certificates of Analysis and/or Materials Safety Data Sheets (MSDS) can facilitate the review of each material. Applications should include the Chemical Abstract Service (CAS) number, if available, of each chemical component. If material chemistry information in a device master file (MAF) will be referenced, manufacturers should include a right to reference letter from the MAF holder. Firms should also document the material composition of the final finished device.

If biocompatibility is not evaluated as described in the guidance “Use of International Standard ISO-10993, ‘Biological Evaluation of Medical Devices Part 1: Evaluation and Testing,’” or if biocompatibility testing identifies a concern, additional material chemistry information may be needed, such as a description of all material chemistry changes expected during the manufacturing of your device.

2. Material physical properties

Inter-layer bonding (adhesion/cohesion) is unique to AM and determines the ultimate structural integrity of the final finished device. As such, material properties known to affect interlayer bonding should be characterized. This information should be representative of the final finished device (subjected to all post-processing, cleaning, and sterilization steps).

If the device is additively manufactured using metal or ceramic, the FDA recommends that firms characterize the grain size and orientation, as well

as phase composition and microstructure. If the AM process results in structural inhomogeneity, microstructural voids, incomplete consolidation, or other microstructural issues, the FDA may require additional mechanical testing to show that these issues do not affect device performance.

If the device is additively manufactured using a polymer, the guidance recommends that you characterize the shore hardness and presence of voids or evidence of incomplete consolidation to ensure that the AM process is creating a device or component with uniform properties.

If your device is additively manufactured using an absorbable material, the FDA recommends that you perform in vitro degradation testing using final finished devices or coupons.

E. Removing Manufacturing Residues and Sterilization

Cleaning process validation and sterilization process validation should account for the complex geometry of the device under worst-case conditions (e.g., greatest amount of residual manufacturing materials for cleaning validation, and a combination of largest surface area, greatest porosity, and most internal voids for sterilization validation).

Where a manufacturing material could reasonably be expected to have an adverse effect on device quality, the manufacturer must establish and maintain procedures for the use and removal of such manufacturing material to ensure that it is removed or limited to an amount that does not adversely affect the device's quality. For devices manufactured using AM, only devices that are cleaned of manufacturing materials should be provided to the end user. The FDA recommends that firms include information in their premarket submissions to indicate that the device is cleaned of manufacturing materials before being provided to the end user. In addition, in light of the challenges posed by the complex geometry of some AM devices, firms should consider sterilizing the device prior to providing the device to the end user.

F. Biocompatibility

The final guidance recommends that firms evaluate the biocompatibility of the final finished device as described in the guidance “Use of International Standard ISO-10993, ‘Biological Evaluation of Medical Devices Part 1: Evaluation and Testing.’”

G. Labeling

Because clinical staff, device manufacturers, or a designated third party might modify the design of each patient-matched device, additional labeling information is recommended for AM devices that are patient-matched. Each patient-matched device should be marked or have accompanying physician labeling included in the packaging to identify the:

- patient identifier,
- use (e.g., left distal femoral surgical guide), and
- final design iteration or version used to produce the device.

For more information, please contact the Barnes & Thornburg LLP attorney with whom you work or the chair of the firm’s Food, Drug and

Device Practice Group, Lynn Tyler at (317) 231-7392 or lynn.tyler@btlaw.com.

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