Technical Considerations for Additive Manufactured Devices

Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Document issued on May 10, 2016.

You should submit comments and suggestions regarding this draft document within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this document, contact the Division of Applied Mechanics at (301) 796-2501, the Division of Orthopedic Devices at (301) 796-5650, or Matthew Di Prima, Ph.D. at (301) 796-2507 or by email matthew.diprima@fda.hhs.gov. For questions about this document regarding CBER-regulated devices, contact the Office of Communication, Outreach, and Development (OCOD) at 1-800-835-4709 or 240-402-8010.

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

Preface

Additional Copies

CDRH

Additional copies are available from the Internet. You may also send an e-mail request to CDRH-Guidance@fda.hhs.gov to receive a copy of the guidance. Please use the document number 1400002 to identify the guidance you are requesting.

CBER

Additional copies are available from the Center for Biologics Evaluation and Research (CBER), by written request, Office of Communication, Outreach, and Development (OCOD), 10903 New Hampshire Ave., Bldg. 71, Room 3128, Silver Spring, MD 20993-0002, or by calling 1-800-835-4709 or 240-402-8010, by email, ocod@fda.hhs.gov or from the Internet at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

Table of Contents

Technical Considerations for Additive Manufactured Devices

Draft Guidance for Industry and Food and Drug Administration Staff

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff or Office responsible for this guidance as listed on the title page.

I. Introduction and Scope

FDA has developed this draft guidance to provide FDA's initial thinking on technical considerations specific to devices using additive manufacturing, the broad category of manufacturing encompassing 3-dimensional (3D) printing. Additive manufacturing (AM) is a process that builds an object by iteratively building 2-dimensional (2D) layers and joining each to the layer below, allowing device manufacturers to rapidly alter designs without the need for retooling and to create complex devices built as a single piece. Rapid technological advancements and increased availability of AM fabrication equipment are encouraging increased investment in the technology and its increased use in medical devices. The purpose of this guidance is to outline technical considerations associated with AM processes, and recommendations for testing and characterization for devices that include at least one AM fabrication step.

This draft guidance is broadly organized into two topic areas; Design and Manufacturing Considerations (Section V) and Device Testing Considerations (Section VI). The Design and Manufacturing Considerations section provides technical considerations that should be addressed as part of fulfilling Quality System (QS) requirements for your device, as determined by the regulatory classification of your device or regulation to which your device is subject, if applicable. While this draft guidance includes manufacturing considerations, it is not intended to comprehensively address all considerations or regulatory requirements to establish a quality system for the manufacturing of your device. The Device Testing

Considerations section describes the type of information that should be provided in premarket notification submissions [510(k)], premarket approval (PMA) applications, humanitarian device exemption (HDE) applications, de novo requests and investigational device exemption (IDE) applications for an AM device. The type of premarket submission that is required for your AM device is determined by the regulatory classification of your device.

Point-of-care device manufacturing may raise additional technical considerations. The recommendations in this guidance should supplement any device-specific recommendations outlined in existing guidance documents or applicable FDA-recognized consensus standards. In addition, this guidance does not address the use or incorporation of biological, cellular, or tissue-based products in AM. Biological, cellular or tissue-based products manufactured using AM technology may necessitate additional regulatory and manufacturing process considerations and/or different regulatory pathways. Therefore, all AM questions pertaining to products containing biologics, cells or tissues should be directed to the Center for Biologics Evaluation and Research (CBER).

This draft guidance is a leap-frog guidance; leap frog guidances are intended to serve as a mechanism by which the Agency can share initial thoughts regarding emerging technologies that are likely to be of public health importance early in product development. This leap-frog guidance represents the Agency's initial thinking, and our recommendations may change as more information becomes available. The Agency encourages manufacturers to engage with the Center for Devices and Radiological Health (CDRH) and/or CBER through the Pre-Submission process to obtain more detailed feedback for additively manufactured medical devices. For more information on Pre-Submissions, please see "Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with FDA Staff - Guidance for Industry and Food and Drug Administration Staff."

For the current edition of the FDA-recognized standards referenced in this document, see the FDA Recognized Consensus Standards Database Website.

FDA's guidance documents, including this guidance, 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

AM is a rapidly growing technology that is frequently used for product research and development in many industries, and for commercial production in some industries (e.g., aerospace, medical devices). While different AM technologies exist, at the time of publication of this draft guidance, the most commonly used technologies in the manufacture

of medical devices are powder fusion, stereolithography, fused filament fabrication, and liquid-based extrusion. Powder bed fusion systems rely on an energy source (laser or electron beam) to selectively melt or sinter a layer of powder, either a metal or polymer, which is then refreshed to create the next layer. Stereolithography systems use a vat of liquid material that is selectively cured using light, either through a laser or projection system, and create new layers by moving the build surface. Fused filament fabrication systems melt a solid filament at the point of deposition, after which the material solidifies in place, and new layers are created by moving the build surface away from the heat source. Liquid-based extrusion systems eject a liquid, which then solidifies (the method of solidification could include light exposure, solvent evaporation, or other chemical process), and new layers are created by moving the build platform away from the deposition tip.

For medical devices, AM has the advantage of facilitating the creation of anatomically-matched devices and surgical instrumentation by using a patient's own medical imaging. Another advantage is the ease in fabricating complex geometric structures, allowing the creation of engineered porous structures, tortuous internal channels, and internal support structures that would not be easily possible using traditional (non-additive) manufacturing approaches. However, the unique aspects of the AM process, such as the layer-wise fabrication process, and the relative lack of medical device history of devices manufactured using AM techniques, pose challenges in determining optimal characterization and assessment methods for the final finished device, as well as optimal process validation and acceptance methods for these devices. The FDA held a public workshop entitled "Additive Manufacturing of Medical Devices: An Interactive Discussion on the Technical Considerations of 3D Printing" on October 8-9, 2014 to discuss these challenges and obtain initial stakeholder input.[1]

The workshop provided a forum for medical device manufacturers, AM companies, and academia to discuss technical considerations for AM medical devices. The workshop focused on five broad themes: (1) materials; (2) design, printing, and post-printing validation; (3) printing characteristics and parameters; (4) physical and mechanical assessment of final devices; and (5) biological considerations of final devices, including cleaning, sterility, and biocompatibility. While a variety of different types of materials can be additively manufactured, workshop participants noted that material control is an important aspect to ensure successful fabrication, and that final device performance is tied to the machine and post-printing processes. The interaction between the material and machine was also discussed in the process validation session, and the need for a robust process validation and acceptance protocol appropriate to the risk profile of the final device was identified. AM design procedures were also discussed, and the importance of having a good understanding of the processes and limits in the design phase was identified. There was general agreement that

[1] http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm397324.htm

printing parameters should be captured and validated for each machine/material combination. The discussion on the physical and mechanical assessment focused heavily on validation of the process and acceptance of devices and components after post-processing. The discussion on the biological considerations revealed that there is a concern across the community regarding how to achieve adequate cleaning, sterility, and biocompatibility of an AM device. Specifically, the challenge of assessing and verifying these issues in porous or internally complex devices was discussed. The feedback obtained at the workshop served as the basis for this draft guidance.

III. Overview

The information, characterization, and testing necessary for a device made through AM may depend on a variety of factors including, but not limited to, whether it is an implant, load bearing, and/or available in pre-specified standard sizes or is patient-matched. This draft guidance outlines technical aspects of an AM device that should be considered through the phases of development, production process, process validation, and final finished device testing. Not all considerations described will be applicable to a single device, given the variety of AM technologies available. Similarly, not all considerations are expected to be addressed in premarket submissions of AM devices. It is anticipated that AM devices will generally follow the same regulatory requirements as the classification and/or regulation to which a non-AM device of the same type is subject to. In rare cases, AM may raise different questions of safety and/or effectiveness. In addition, this draft guidance only addresses manufacturing considerations specific to the AM process. If it is unclear what technical information should be provided in a premarket submission for an AM device, we strongly encourage manufacturers to engage with FDA through the Pre-Submission process to obtain more detailed feedback. For more information on Pre-Submissions, please see "Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with FDA Staff - Guidance for Industry and Food and Drug Administration Staff."

The overall AM process and the related sections in this draft guidance are shown in the flow chart below. The first step is the design process, which can include a standard design with discrete pre-specified sizes and models, or a patient-matched device designed from a patient's own medical images. Once the device design has been created, the software workflow phase begins, where the device design is further processed to prepare it for printing, printing parameters are optimized, and the build file is converted into a machine-ready format. Concurrently with this step, material controls are established for materials used in the printing of the device. After printing is complete, post-processing of the built device or component (e.g., cleaning, annealing, post-printing machining, sterilization) takes place. After post-processing, the final finished device is ready for testing and characterization. Your quality system should be applied across all of these processes.

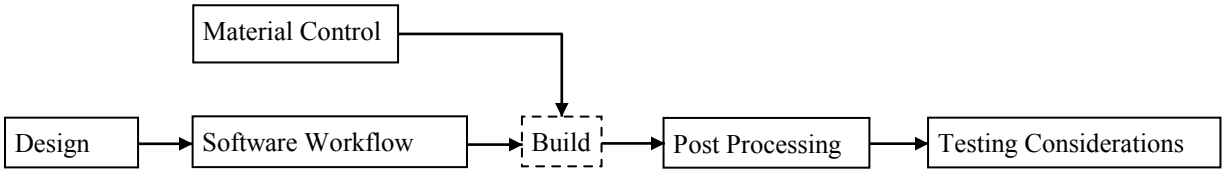

Figure 1: Flow chart of the additive manufacturing process

IV Definitions

The following terms are defined for the purpose of this draft guidance and may not be applicable to any other documents issued by the FDA.

Build Cycle – a single cycle in which one or more devices or components are built up in layers in the process chamber of the machine.[2]

Build Preparation Software – the software used to convert the digital design to a format that can be used to build a device or component through an AM process. This may include multiple software components.

Design Manipulation Software – the computer program that allows a medical device design to be modified for specific circumstances (e.g., patient-matching).

Lot or Batch – one or more components or finished devices that consist of a single type, model, class, size, composition, or software version that are manufactured under essentially the same conditions and that are intended to have uniform characteristics and quality within specified limits.[3]

Machine – a system including the hardware, machine control software, required set-up software, and peripheral accessories necessary to complete a build cycle. [4]

Quality – the totality of features and characteristics that bear on the ability of a device to satisfy fitness for use, including safety and performance.[5]

---

[2]ASTM F2924 *Standard Specification for Additive Manufacturing Titanium-6 Aluminum-4 Vanadium with Powder Bed Fusion*

[3]21 CFR 820.3(m)

[4]ASTM F2924 *Standard Specification for Additive Manufacturing Titanium-6 Aluminum-4 Vanadium with Powder Bed Fusion*

V Design and Manufacturing Process Considerations

This section highlights technical considerations that should be addressed as part of fulfilling Quality System (QS) requirements for your device. However, this draft guidance is not intended to comprehensively address all regulatory requirements for a quality system. For class II and class III devices and select class I devices, manufacturers must establish and maintain procedures to control the design of the device in order 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.[6] Alternatively, where the results of a process cannot be fully verified by subsequent inspection and test, the process must be validated with a high degree of assurance and approved according to established procedures.[7] FDA interprets these regulations to require manufacturers to establish procedures, including validation of the manufacturing process of AM devices, to ensure that the device can perform as intended. Please note that exemption from the requirement to submit a premarket notification (510(k)) does not mean a device is exempt from compliance with QS requirements. Some devices are specifically exempted by regulation from most QS requirements. Manufacturers should refer to applicable regulations for their specific device type to determine what QS requirements apply. In this section, the use of the terms "document," "describe," and "identify" refers to documentation requirements according to the QS regulations and premarket submission requirements for manufacturing information determined by the regulation of a specific device type or classification, regardless of the method of manufacture.

There are several AM technologies and different combinations of processing steps which can be used with each technology to build a device. Therefore, it is important to clearly identify each step in the printing process. A production flow diagram that identifies all critical steps involved in the manufacturing of the device, from the initial device design to the post-processing of the final device, can help ensure product quality. In addition, a high-level summary of each critical manufacturing process step may be helpful in documenting the AM process used. The characterization of each process step should include, but need not be limited to, a description of the process and identification of the process parameters and output specifications. Since processes that optimize one design parameter may influence another, information on processing steps should demonstrate your understanding of these trade-offs. Additionally, the cumulative effects of prior processes on the final finished device or

---

[5] 21 CFR 820.3(s)
[6] 21 CFR 820.75(b)
[7] 21 CFR 820.75(a)

component should be incorporated into the development of each process step and documented. The effects of the different steps in the AM processes can be seen in final device testing; however, determining the root cause of failures from manufacturing defects can be very difficult without a clear understanding of each step. For example, the ratio of recycled to virgin powder can affect melting properties, which affects the energy needed to create consistent bonding between layers, which in turn affects final mechanical properties. Similarly, risks identified for each step of the manufacturing process, as well as mitigations of these risks, should be documented. It is important to use all reasonably obtainable knowledge about your specific machine's capabilities to ensure the manufacturing process outputs meet defined requirements.[8] Quantitative knowledge of the machine's capabilities and limitations can be gained through test builds, worst-case builds, or process validation (See section V.E Process Validation and Acceptance Activities and section VI.B Mechanical Testing for more information).

As with traditional manufacturing methods, design requirements drive the processes that can be used to reliably produce the device. It is therefore important to clearly identify key design parameters for your device, including, but not limited to, size range and available design or configuration options (e.g., range of angles between the trunnion and stem of the femoral component of a hip arthroplasty device).

While this section includes manufacturing considerations, it is not intended to comprehensively address all considerations or regulatory requirements for establishing a quality system for the manufacturing of your device. Aspects of the "Global Harmonization Task Force Process Validation Guidance" may be helpful in developing process validation procedures. Additional information on design controls can be found in the "Design Control Guidance For Medical Device Manufacturers." For general questions regarding quality system regulations, contact the Division of Industry and Consumer Education (DICE), Office of Communication and Education, at 1-800-638-2041 or 301-796-7100 or DICE@fda.hhs.gov.

A. Device Design

(1) Standard-Sized Device Design

Standard-sized devices, or devices offered in pre-established discrete sizes, are often made by AM if they include features that are too complex to be made using other techniques. The innovative potential of AM introduces variability into the design process that may not be present when using other manufacturing

[8]ISO 14971 *Medical devices - Applications of risk management to medical devices*

techniques. Specifically, we recommend that you compare the minimum possible feature size of your AM technique, in addition to the manufacturing tolerances of the machine, to the desired feature sizes of your final finished device. This is to ensure that devices and components of the desired dimensional specifications can be reliably built using the chosen additive technology. Dimensional specifications for the final device or component, as well as manufacturing tolerances of the machine, should be documented. Pixelation of features, where smooth edges become stepped, can lead to inaccuracies in final finished device dimensions. Any pixelation of features caused by mismatch of machine resolution and model resolution should be identified.

(2) Patient-Matched Device Design

Patient-matched devices can be based on a standard-sized template model that is matched to a patient's anatomy. Patient-matching can be accomplished by techniques such as scaling of the device using one or more anatomic references, or by using the full anatomic features from patient imaging. Note that while patient-matched or patient-specific devices are sometimes colloquially referred to as "customized" devices, they are not custom devices meeting the FD&C Act custom device exemption requirements unless they comply with all of the criteria of section 520(b). For further information on custom device exemptions, please refer to the Custom Device Exemptions guidance.

Patient-matched device designs may be modified either directly by clinical staff, the device manufacturer, or a third party in response to clinical inputs. These inputs may be acquired from individual measurements, clinical assessments, patient imaging, or a combination thereof. Alterations to the final device, and the methods used to make the alterations, may have direct consequences to the patient. Therefore, you should clearly identify clinically-relevant design parameters, the range (min/max) for these parameters, and which of these parameters can be modified for patient-matching.

Considerations for standard-sized devices are applicable for patient-matched devices. In addition, for patient-matched AM devices, we recommend that you address the following, if applicable:

i. Effects of imaging

Many AM devices and components are derived from medical imaging data. Not every medical device will need the same level of anatomic matching or imaging accuracy for optimal device performance. Several factors 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.

If the device relies on anatomic features that are not accurately imaged or are not consistent over time, then the final device may not fit the patient. However, small changes in size or geometry may be difficult to identify during visual inspection of the device or through evaluation of patient imaging, and the mismatch may only be identified during device use. Process validation (see section V.E.1) is especially important to prevent these situations. In addition, for devices intended to be fitted to or matched to soft tissues and non-rigid structures, deformation of the tissue is likely to impact the worst-case size and placement. Therefore, it is important to note the range of deformation experienced by the target location or tissue compared to the reference image.

You should also consider the potential time constraints associated with producing an AM device based on the intended use of your device. Specifically, when the device is intended to match a patient's anatomy, and that 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 (see section VI.G Additional Labeling Considerations). Many implantable devices and their patient-matched accessories depend on the patient's anatomy being identical to the recorded images in order for the device to function as intended. Therefore, the labeled shelf life of the device should account for the potential for time-dependent changes to the patient anatomy before the device is used.

ii. Interacting with design models

Patient-matched devices are often made by altering the features of a standard-sized device for each patient within a pre-determined range of device designs and size limits. This is typically accomplished through the use of anatomic-matching or design manipulation software that may be developed specifically for the AM device or through the use of other third party software. Patient-matching may also be accomplished by manual methods using specific measurements on radiographs or key anatomic landmark measurements. 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. We recommend that the design manipulation software identify the iteration of the design the user is making changes to. You should also identify all medical devices and accessories that the design manipulation software is validated to work with.

B. Software Workflow

(1) File Format Conversions

AM involves interaction between several software packages, often from different manufacturers, which requires files to be compatible across the different software applications used. Patient images (e.g., computed tomography (CT) or magnetic resonance (MR) imaging), design manipulation software for patient-matching, digital point clouds and meshes (e.g., Additive Manufacturing (AMF), STereoLithography (STL), 3D Graphic (STP) file formats), and machine-readable files (e.g., sliced files, build files, g-code) each have their own standards, coordinate systems, and default parameters. Errors in file conversion can negatively impact final finished device and component properties, such as dimensions and geometry. Patient-matched devices that follow the patient anatomy precisely are especially vulnerable to these errors because anatomic curves are typically geometrically or mathematically complex and can create difficulties when calculating conversions. Additionally, for patient-matched devices, all of the file conversion steps are typically performed for every device, whereas for a standard-sized device, most of the file conversion steps would be performed once during the design phase. Therefore, we recommend that you test all file conversion steps with simulated worst-case scenarios to ensure expected performance, especially for patient-matched devices. Factors that may cause unexpected conversion failures, such as changes to the software used, may trigger the need for revalidation (see section V.E.2 Revalidation).

When possible, final device files for printing should be maintained and archived in robust, standardized formats that are able to store AM-specific information, such as the Additive Manufacturing File format (AMF) described in the ISO/ASTM 52915 *Standard specification for additive manufacturing file format (AMF)*. This file format should include material information and the location of objects in a build volume and have high geometric fidelity (e.g., curved patches).

(2) Digital Device Design to Physical Device

When a digital device design is finalized, additional preparatory processes are needed before the device can be additively manufactured. This is commonly accomplished using build preparation software. These processes can generally be divided into four steps: 1) build volume placement, 2) addition of support material, 3) slicing, and 4) creating build paths.

i. Build Volume Placement

Placement and orientation of devices or components within the build volume is integral to individual device or component quality. The distance between each device or component can affect the material properties (e.g., poor consolidation or curing), surface finish, and ease of post-processing. Orientation of each device or component can also impact its functional performance by affecting the anisotropic properties of the device or component. Similarly, all machines have areas of the build volume where they function optimally and areas where they do not function optimally. For example, printing may be sub-optimal in the regions near the outer edge of the build volume and optimal at the center. The affected region may be different for every machine, even between machines of the same model.

ii. Addition of Support Material

Some types of AM require temporary support structures for certain design features during printing due to the layer-by-layer printing process. The location, type, and number of supports can affect the geometric accuracy and mechanical properties of the final finished device or component. Each AM technology has different needs for support material that must be met for the successful printing of a device. For example, the critical overhang angle may be different for a stereolithography machine, extrusion-based machine, and a metal powder bed fusion machine. Automated algorithms are often used to choose the location and number of supports. However, geometric complexities or printing limits often necessitate further manual intervention. Therefore, if your AM process requires support material, we recommend that you analyze the geometry and other requirements that could be affected by adding supports. Some common structures that may need support are:

- overhangs,
- high aspect ratio features that protrude from the main body of the device or component,
- internal features (e.g., voids, channels), and
- thin features prone to warping.

Support material can be removed physically (e.g., abrasion, melting) or by chemical means. Support material that is physically removed may leave surface defects that should be addressed in the post-processing phase of production. Support material that is chemically removed may leave residue on or within the built device or component. Cleaning processes should ensure that residues are removed (see section VI.E Cleaning and Sterilization). Information about how support material will be used and processed should be included in the Device Master Record (DMR), including documents such as work flow diagrams and work instructions.

iii. Slicing

Most AM techniques use a layer-wise printing process to fabricate components. This necessitates slicing the models into layers. Nominal layer thickness is determined by the machine specification and software capabilities. However, technical characteristics of the machine and physical properties of the material may influence the achievable layer thickness. The surface texture of a device or component, bonding between and curing of each layer, and sensitivity to power fluctuations can all be affected by the choice of layer thickness. For example, the depth of material cured in a stereolithography system is primarily controlled by the energy density and additives in the liquid polymer. If the energy density is changed to reduce layer thickness and the additives are not adjusted properly, the layers may not cure or bond together completely. For systems where layers are created by melting the material, the layer thickness can similarly influence the energy needed to create a uniform melt pool to enable bonding to the layer below.

Your choice of layer thickness should be documented, and reflect a balance among the above-mentioned effects, accuracy, quality, and printing speed.

iv. Build Paths

The build path, the path traced by the energy or material delivery system (e.g., laser or extruder), can impact the quality of the final finished device or component. For example, if the delivery system sweeps from left to right on the build volume, then makes the next pass from right to left, one side of the device or component has more time to cool or harden. Similarly, the space between each line of the build path and the path speed will change the amount of melting and re-melting that the boundaries of each line of material will experience. In addition, the build path will result in an orientation or anisotropy in the device or component. Therefore, it is important to maintain consistency of the build path between identical devices and components. If more than one build path is used, each build path should be documented. We

also recommend that you assess whether differences in the build path significantly affect the performance of each component or device.

When the path of the delivery system is generated by the build preparation software, the fill density of a component can be specified separately from patterns in the component's geometry. For example, if the geometry shows a solid wall, it is possible to fill that solid space with a sparse honeycomb instead. These voids are easily formed with an extrusion-based machine. The fill density of parts that are not fully dense (i.e., not a solid) should be documented. If a non-solid fill density is used, we recommend that you identify whether internal voids are externally accessible or sealed. If the voids are sealed, you should identify the fluid or gas that fills the voids. The risk associated with patient exposure to the materials in the voids should also be assessed.

v. Machine Parameters and Environmental Conditions

Each AM technology and machine model has a unique set of parameters and settings that can be modified by the device manufacturer and a unique set of those that are configured at the time of calibration (typically by the machine manufacturer). Maintaining proper calibration and performing preventative maintenance have been identified as key factors to achieve low rejection rates of devices and components from an individual machine.

Environmental conditions within the build volume can also affect the part quality. For machines without a self-contained build volume, the ambient temperature, atmospheric composition and flow patterns can impact solidification/polymerization rate, layer bonding, and the final mechanical properties of the component. Therefore, it is critical to establish and maintain procedures to adequately control environmental conditions within the build volume.

Optimal settings and parameters for a single model of a machine can vary greatly when printing different devices or components. They can likewise vary greatly between one machine of the same model and another when printing the same devices or components. Some parameters that can be modified by the device manufacturer and may have a significant impact on the device or component quality include, but are not limited to:

- instantaneous power of the energy delivery system (e.g., temperature gradients of deposition nozzle for fused filament systems, energy density of laser or electron beam for powder bed fusion or stereolithography),

- build speed or beam speed,
- build path,
- total energy density, and
- focal point or nozzle diameter.

Machine parameters should be documented, and the machine should be qualified for use in its installation location. Aspects of the "Global Harmonization Task Force Process Validation Guidance" also address Installation Qualification.

C. Material Controls

(1) Starting Material

In the AM process, the starting material may undergo significant physical and/or chemical changes. As such, the starting material can have a significant effect on the success of the build cycle, as well as on the properties of the final finished device. It is therefore, important to document the following information regarding each starting material used, as well as any processing aids, additives, and cross-linkers used:

- 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.

The specifications for incoming materials and test methods should be based on the AM technology used (i.e., material specifications will be different for powder-based vs. stereolithography machines). Examples of specifications for commonly used material types and machine technologies may include, but are not limited to:

- if the material is a solid: particle size and size distribution for powders or filament diameter and diametric tolerances for filaments,
- if the material is a fluid: viscosity or viscoelasticity, pH, ionic strength, and pot life,
- if the material is a polymer or monomer mixture: composition, purity, water content, molecular formula, chemical structure, molecular weight, molecular weight distribution, glass transition temperatures, and melting and crystallization point temperatures,

- if the material is a metal, metal alloy, or ceramic: chemical composition and purity,
- if the material is of animal origin, refer to: "Medical Devices Containing Materials Derived from Animal Sources (Except for In Vitro Diagnostic Devices)."

In addition, when any material specification is changed, the effect on the build process and the final device should be well understood and documented.

(2) Material Recycling

Some additive manufacturing approaches (e.g., powder bed fusion, stereolithography) allow efficient use of raw material by recycling the material that is not incorporated into the device (e.g., unsintered powder or uncured resin). However, the reused material could be exposed to conditions (e.g., heat, oxygen, humidity, ultraviolet energy) that may alter it from the virgin state. Therefore, we recommend that you describe the material recycling process, which may include, but is not limited to, a description of recycling processes such as filtering recycled material, or monitoring for changes in chemistry, oxygen, or water content. We also recommend that you document evidence that material recycling does not adversely affect the final device. This may include an assessment of the recycling protocol by conducting studies on the effect of material recycling on the properties of the final finished device (see section V.E.1 Process Validation).

D. Post-Processing

Final device performance and material properties can be affected by post-processing steps of AM (i.e., manufacturing steps occurring after the printing process). These steps could range from cleaning excess starting material from the device, through annealing the device to relieve residual stress, to final machining. All post-processing steps should be documented and include a discussion of the effects of post-processing on the materials used and the final device. We recommend that you identify any potentially detrimental effects of post-processing and describe mitigations implemented. For example, while annealing will remove residual stress to prevent warping, it may lower the strength of the device, which could be mitigated by a subsequent surface hardening process or by altering the design to accommodate a lower material strength.

Devices that are intended for applications where fatigue is a factor may require minimum surface finish or roughness to reduce the chance of failure. The desired surface roughness can often be achieved through various post-processing steps (e.g.,

mechanical polishing); however, hard-to-reach spaces may remain in the as-built state. These spaces should be assessed for their effects on mechanical performance (including fatigue) of the device or component.

E. Process Validation and Acceptance Activities

(1) Process Validation

Device quality, such as feature geometry, overall dimensions, material characteristics, and mechanical properties, are impacted by AM process parameters, process steps, and raw material properties, as described in the sections above. In addition, quality may vary when identical devices or components are built using different machines, even when the same machine model, parameters, process steps, and raw materials are used. Therefore, knowledge of how the variability of each input parameter and processing step affects the final finished device or component is critical to ensuring part quality. 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.[9] Software also must be validated for its intended use according to an established protocol[10] (i.e., software workflow).

For validated processes, the monitoring and control methods and data must be documented.[11] Methods for ensuring the consistency of quality could include:

- in-process monitoring[12] of parameters such as:
  - temperature at the beam focus,
  - melt pool size,
  - build-space environmental conditions (e.g., temperature, pressure, humidity),
  - power of the energy delivery system (e.g., laser, electron beam, extruder), or
  - status of mechanical elements of the printing system (e.g., recoater, gantry);

[9] See 21 CFR 820.75(a)
[10] See21 CFR 820.70(i), and "General Principles of Software Validation; Final Guidance for Industry and Staff."
[11] See 21 CFR 820.75(b)(2)
[12] In-process monitoring may also be helpful for processes that are not validated, but is not required.

- manual or automated visual inspection with defined acceptance criteria;
- non-destructive evaluation (see section V.E.3 Acceptance Activities); and
- test coupon evaluation (see section V.E.4 Test Coupons).

Test methods used for process monitoring and control must be validated.[13] For example, analysis should be conducted to confirm that test coupons used are representative of the final finished device or component and representative of a certain area within the build volume.

A single failed component or device in a build cycle may not necessitate all devices or components within that build cycle to also be rejected. The criteria for determining whether to reject a single device or component, or the entire build, should be established before testing.

(2) Revalidation

Changes to the manufacturing process or process deviations can trigger the need for revalidation, and these changes or deviations should be identified for each process. Some examples of triggers for revalidation specific to AM may include:

- certain software changes (e.g., change or update of build preparation software),
- changes in material (e.g., supplier, incoming material specification, ratio of recycled powder) or material handling,
- change in the spacing or orientation of devices or components in the build volume,
- changes to the software workflow (see section V.B.2 Digital Device Design to Physical Device),
- physically moving the machine to a new location, and
- changes to post-processing steps or parameters.

(3) Acceptance Activities

Acceptance activities are integral to process control. Many AM technologies can produce more than one device or component simultaneously on different locations in the build volume. These devices or components can be copies of a single design or different designs. This poses a unique challenge in ensuring repeatability and consistency within a build cycle and across lots.

[13] See 820.72(a) and 820.250(a)

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. Techniques include, but are not limited to:

- ultrasound,
- computed tomography (CT) or micro-CT,
- X-ray (in cases where the geometry is simple),
- confocal microscopy, and
- hyperspectral imaging.

Some techniques are not suitable for some materials or designs. The ASTM Committee on Nondestructive Testing has published general NDE testing protocols and the ASTM Committee on Additive Manufacturing Technologies has developed protocols specific to AM[14] If an NDE technique is used in your process validation or acceptance activities, the choice of technique should be discussed and documented.

(4) Test Coupons

A test coupon is a representative test sample of the device or component. The design of test coupons and placement within the build volume is especially important for AM. Coupons can be simple shapes suitable for destructive mechanical testing, or they may contain one or more structural features (e.g., surface porosity, internal channels) representative of the component or device that can be assessed using destructive techniques. We recommend that coupons be used for your process validation, and to identify worst-case conditions in your manufacturing process (e.g., worst-case orientation and location in build volume). Test coupons can also be used for in-process monitoring by placing them in build volume locations that are known to have the worst-case outputs. These test coupons can confirm that the components or devices built in the same build cycle will meet specifications if the test coupons also meet these specifications. For example, test coupons may be placed at the edges of the build volume if edges are known to have less optimal build quality. They may also be placed randomly in between components or devices to produce a sampling of the build quality. Data

[14] http://www.astm.org/COMMIT/SUBCOMMIT/F42.htm

to demonstrate that test coupons are representative of the components, in-process devices, or finished devices should be documented.

F. Quality Data

The analysis of sources of quality data to identify existing and potential causes of nonconforming product, or other quality problems is an essential part of any quality system. For devices produced by AM, it is important to consider whether it is necessary to keep track of the location in the build volume where a device or component was built. This will depend on information obtained during process validation activities and design specifications. For example, if process validation demonstrated that quality is not affected by location in the build volume, it may not be necessary to be able to keep track of the build volume location for each device. This level of specificity is important in identifying possible causes of failure when multiple different components or devices are made in the same build volume at the same time. Therefore, you 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.

VI Device Testing Considerations

The following section contains a description of the type of information that we recommend that you include in a premarket submission of a device made using AM. The type and amount of data to support a substantial equivalence determination or approval will vary depending on the intended use, risk profile, and classification and/or regulation for the device type. In addition, the type of information needed for a device made through AM may also depend on a variety of factors, including, but not limited to, whether it is an implant, load bearing, and/or available in pre-specified standard sizes or is patient-matched. Not all considerations described will be applicable to a single device, given the variety of devices that can be made by AM and the AM technologies available. In general, if the type of characterization or performance testing outlined in each of the sub-sections below is needed for a device made using non-AM techniques, the information should also be provided for an AM device of the same device type. If you have specific questions regarding the information to support a premarket application for an AM device, please contact the relevant review division in CDRH or contact CBER for products containing biologics, cells or tissues.

A. Device Description

AM facilitates the creation of intermediate and customized device sizes. Patient-matched devices are a good example of this application. Since these devices may not

have discrete sizes, such as small, medium, and large, we recommend that you identify the range of dimensions for your device. In addition, you should describe any design variations, for example the amount of anatomical coverage for a cranioplasty plate. Any critical dimensions or features that are intended to be altered to match a patient should be clearly identified, and the range of allowable values for these parameters should also be identified. Since each type of AM technology has different technical considerations, you should describe the type of AM technology used to build your device. In addition, because AM use for medical devices is relatively new, we recommend that you include a flow chart describing your AM process, including post-processing, in order to help determine if additional assessments are needed.

Due to the generally complex geometry of AM devices, we recommend that critical features of the device be clearly described in the device description and identified in technical drawings. For example, the location and thickness of porous scaffolding should be described, as these features may have reduced mechanical properties in comparison to a solid material. In the technical drawings of your device we recommend that you identify components made using AM.

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. Depending on the device type, these may include material property testing such as, but not limited to, modulus, yield strength, ultimate strength, creep/viscoelasticity, fatigue, and abrasive wear. Performance testing should be conducted on final finished devices subjected to all post-processing, cleaning, and sterilization steps or on coupons, if the coupon undergoes identical processing as the final finished device. In addition, the worst-case combinations of dimensions and features (e.g., holes, supports, porous regions) should be considered when determining the worst-case devices for performance testing. You should also provide a discussion of how the worst-case devices were selected for each performance test conducted.

Due to the nature of AM, devices will have an orientation (i.e., anisotropy) relative to the build direction and location within the build space. The orientation and build location can affect the final properties and should be considered when conducting device mechanical testing. Specifically, the build orientation (including worst-case orientation) of devices or components should be identified for each performance test. If the orientation changes with device size or design, the worst-case orientation should be identified for each configuration. Since the effect of orientation can vary based on the manufacturing technology used, a baseline study of the machine/material combination used may be helpful in determining the degree to which the build

orientation will affect mechanical properties. Coupons may be used for material property assessments if the coupon undergoes identical processing (including post-printing processes, cleaning, and sterilization) to that of the final finished device. This information can be used to aid in the selection of worst-case samples with respect to orientation.

In addition, for some AM machines, the location within the build space can have an effect on mechanical properties.[15] For example, for a powder bed system, the difference in distance from the energy source to different locations in the build space (e.g., center vs. corner) could lead to variability in the mechanical properties of devices built in those locations. To determine whether build location has a significant effect on device characteristics or performance (including fatigue strength), we recommend that you perform a baseline study of your machine/material combination (see section V.E.1 Process Validation). The use of coupons for your baseline study is recommended. If there is a significant effect, build location should be considered in the identification of worst-case samples for mechanical testing.

Since mechanical properties of the device may be impacted by orientation and location, it is important to ensure that production processes are properly developed, conducted, controlled, and monitored to ensure devices or components are not adversely affected by fabrication orientation. The information on the impact of orientation and location may be leveraged from process validation described in section V.E. Process Validation and Acceptance Activities.

C. Dimensional Measurements

Similar to mechanical properties, device dimensions may be affected by orientation and location within the build space. Therefore, we recommend that you specify the dimensional tolerances and perform dimensional measurements for each additively manufactured component. Samples selected for dimensional measurements should address variability due to orientation and build location if baseline studies show a dependence on these parameters. To demonstrate consistency and reproducibility between build cycles, dimensional measurements should be made on samples from multiple build cycles, and a justification should be provided on the sampling scheme used. Alternatively, you may use process validation information to demonstrate that there is negligible variability between build cycles.

[15] ASTM F3122 "*Standard Guide for Evaluating Mechanical Properties of Metal Materials Made via Additive Manufacturing Processes*"

While we are aware of the potential effects of orientation and build location on mechanical properties and dimensional tolerances, there may be other properties that could be affected based on the intended use and technological characteristics of the device.

D. Material Characterization

(1) Material Chemistry

Since the AM process creates the final material or alters the starting material during the process, all materials involved in the manufacturing of the device should be identified. As noted in section V.C Material Controls, this information should include 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. The Chemical Abstract Service (CAS) number, if available, of each chemical component should be provided. If material chemistry information in a device master file (MAF) will be referenced, you should include a right to reference letter from the MAF holder in your premarket submission.[16] You should also document the chemical composition of the final finished device.

Given the iterative nature of AM, the starting material can be exposed to partial re-melting and solidification processes multiple times, which may result in unexpected or undesired material chemistries for some polymer systems. Therefore, 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. In addition, based on this description and the material/machine type used, it may also be necessary to provide additional information or testing for polymers to ensure that there are no unintentionally formed chemical entities that could pose a risk to patient health.

(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

[16] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/ucm142714.htm

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). Material properties can be determined from the final device or by using coupons. If coupons are used, a description of the coupon and a justification for why coupon testing is representative of the final device should be provided.

If your device is additively manufactured using metal or ceramic, we recommend that you 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, additional mechanical testing may be needed to show that these issues do not affect device performance.

If your device is additively manufactured using a polymer, we recommend 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. For AM processes that utilize polymer crosslinking, the percent crosslinking and degree of curing should be evaluated to ensure that the AM process results in a material that is fully cured and has uniform properties. For systems using a crystalline or semi-crystalline material, crystallinity and crystalline morphology should be characterized to ensure that the AM process is not adversely altering the polymer structure and subsequently altering the performance (e.g., creep, material transparency) of the final device. For hydrogel materials, the percent water swelling or water content of the material should be reported to ensure that that the AM process has not adversely affected the materials' ability to uptake water.

If your device is additively manufactured using an absorbable material, we recommend that you perform *in vitro* degradation testing using final finished devices or coupons. If coupons are used, they should be representative of your final finished device in terms of both processing and properties (e.g., surface-to-volume ratio, crystallinity). This will establish whether AM has an adverse effect on the degradation profile of the material.

E. Cleaning and Sterilization

AM facilitates the creation of devices with complex geometries, such as engineered porosity, honeycomb structures, channels, and internal voids or cavities that cannot be produced by traditional manufacturing methods. Such complex geometries in additively manufactured devices are expected to increase the difficulty for cleaning and sterilization due to the likelihood of increased surface area, generation of

extensive tortuous pathways, and creation of internal voids with limited or no access. Additionally, AM allows porous structures to be produced earlier in the manufacturing process than traditional methods, which could result in greater soiling of those porous structures. Therefore, cleaning process validation and sterilization process validation should account for the complex geometry of your 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). Manufacturing material means any material or substance used in or used to facilitate the manufacturing process, a concomitant constituent, or a byproduct constituent produced during the manufacturing process that is present in or on the final finished device as a residue or impurity and not by design or intent of the manufacturer.[17] There is also an increased risk of residual manufacturing material, such as excess starting material or support material, remaining on the final finished device. Since residual manufacturing material may negatively impact the performance of the device, you should describe how the cleaning process used ensures adequate removal of residual manufacturing materials as part of the cleaning validation process. Note that for complex geometries and trapped volumes, destructive testing may be needed to properly validate the cleaning method. In addition, we recommend using final finished devices for validation of the cleaning process, and final finished devices after they have undergone the cleaning process for validation of the sterilization process. For additional information on sterilization, see "Submission and Review of Sterility Information in Premarket Notification (510(k)) Submissions for Devices Labeled as Sterile - Guidance for Industry and FDA Staff."

It is important to note that many end user facilities may not have routine access to the equipment or materials needed to implement cleaning procedures that are designed to remove residual manufacturing materials and are likely not to have personnel who are adequately trained to perform cleaning procedures to remove residual manufacturing materials. In addition, 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. 21 CFR 820.70(h). Therefore, for devices manufactured using AM, only devices that are cleaned of manufacturing materials should be provided to the end user. We recommend that you include information in your premarket submission to indicate that your device is cleaned of manufacturing materials before being provided to the end user. In addition, due to the challenges posed by the complex geometry of

[17] See 21 CFR 820.3(p)

some AM devices, you should consider sterilizing your device prior to providing the device to the end user.

If additively manufacturing a reusable medical device involves reprocessing in health care facilities, we recommend the inclusion of reprocessing instructions in your device labeling. Please refer to the guidance, "Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling - Guidance for Industry and Food and Drug Administration Staff."

F. Biocompatibility

We recommend that you 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.'" If chemical additives with known toxicities are used (e.g., certain additives, catalysts, binding and curing agents, uncured monomers, plasticizers), additional information may be necessary.

G. Additional Labeling Considerations

Device labeling should be developed in accordance with applicable regulations, device-specific guidance documents, and consensus standards. Since clinical staff, device manufacturers, or a designated 3rd 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,
- details identifying use, such as anatomical location (e.g., left distal femoral surgical guide), and
- final design iteration or version used to produce the device.

The expiration date for a patient-matched device may be driven by the patient imaging date or the design finalization date rather than the standard methods of determining device shelf life (see section V.A.2 Patient-Matched Device Design). In addition, it is possible that the patient may have experienced events between the time of imaging and surgery (e.g. additional trauma) that could impact performance of the device. Therefore, we recommend that you include a precaution in your labeling that the patient should be surveyed for potential anatomical changes prior to the procedure.