3D Printing of Medical Devices: The Regulatory Challenges for Manufacturers

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White Paper
April 2018

Introduction

Medical devices created by three-dimensional (3D) printing are increasingly prevalent as manufacturers embrace the underlying technology. As such, the Food and Drug Administration (FDA) recently released the guidance, "Technical Considerations for Additive Manufactured Medical Devices," to provide initial thoughts regarding this emerging technology. (Note: The FDA uses the term "Additive Manufacturing" instead of 3D printing when referring to the manufacturing process of devices created by these processes.) Manufacturers intending to market 3D devices in the US should be aware of this guidance and understand FDA's concerns related to the technology.

Discussion

What is 3D Printing Technology?

3D Printing is a type of manufacturing that uses instructions in a digital file to create an object. The 3D printer deposits or fuses materials in layers based on the instructions given from the digital file. Materials most commonly used in 3D printing of devices include powder versions of ceramics, plastics, and metal. More recently, the 3D-printing technology has been expanded to include the use of using human tissues and components to create medical devices.

Advantages of 3D printing include the ability to create surgical instrumentation and devices anatomically tailored to fit a patient (i.e., patient-matched devices or PMD), and to create devices that have complex geometries such as those with a honeycomb structure, or those with channels, internal voids or cavities.

Medical applications for 3D printing include the construction of prosthetics, implants, orthopedic and orthotic devices (e.g., joint replacement, casts, braces, and splints), and surgical instruments tailored for a patient's specific anatomy. 3D printing has also been used for creating anatomical components needed for respiratory, spinal, craniofacial, and dental repair.

3D printing technology has expanded to include the use of human tissues and components to create medical devices. 3D printing using cells, and biomaterials, to create a customized device, is known as "bioprinting." Bioprinting to create tissues and organs (is being explored. Researchers have used 3D printers to create a heart valve, spinal disk, a knee meniscus, an artificial ear, and other types of cartilage and bone.

3D Printing Basics

Patient-match devices are created by conversion of a two-dimensional (2D) radiographic image of a patient into a digital 3D print file. In other words, imaging of the patient's anatomy is used by software that transfers and manipulates the data that then converts in into a digital file with specifications for the creation of a "customized" device.

The digital files generate specific instructions for the 3D printer to fabricate a medical device; the shape, texture, color, and thickness of an object is proscribed. 3D printing uses the layering technique to create an object: successive layers of raw material are added to the prior one until the device is completed.

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Bioprinting uses "bioink" (i.e., droplets of living cells or biomaterials) onto a substrate according to digital instructions, too. Different cell types can be deposited by different printheads (e.g., blood or muscle cells, or cells specific to a type of organ, etc.) enabling cellular tissues and organs to be comprised of multiple cells and types of tissue similar to those found in the human body. In addition, devices of cellular materials can be created that are strong, stiff, and lightweight (e.g., lattice structures for cranial support). Note: a biomaterial is a substance that is compatible with the human body and has been created for a medical purpose to interact with a specific biological system.

The most common types of technology used in 3D printing are:

- Material Extrusion: the printing material (e.g., plastic filament) is heated until it is a liquid, it is then extruded through the print nozzle and deposited in layers with each layer bonding to the one below it.
- Material Jetting: material is deposited through an inkjet printer head; this process usually uses plastic which is cured with light.
- Binder Jetting: a thin layer of powder is applied to the build platform; a binding solution is sprayed onto the powder to fuse it.
- Powder Bed Fusion: a thin layer of powder is applied to the build platform; subsequent layers are fused to form a solid mass of material by using a heat source (e.g., laser or electron beam).
- Directed Energy Deposition: wire or powder material is deposited in thin layers and melted using a high-energy source.
- Sheet Lamination: thin sheets of material are bonded by using adhesives, low-temperature heat sources or other forms of energy;
- Vat Photopolymerization: uses a liquid resin that is cured by light.

Bioprinting usually involve one of three types of printers:

- Inkjet printers – this is used for large-scale products needed quickly. The "drop-on-demand" printer prints materials in precise amounts
- Laser-assisted printers – these printers provide high-resolution printing; and
- Extrusion printers – these printers print cells layer-by-layer to create 3D constructs. Note: extrusion printers may also use hydrogels infused with cells to create a finished device.

Benefits of Using 3D Printing

Advantages of using 3D printing to manufacture medical devices not only include the benefits mentioned above – there are also benefits to the patient, the user, and the manufacturer of 3D printing devices.

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Benefits to the Patient

Depending of the type of device, surgical instrument and type of procedure, benefits to the patient may include superior comfort, less time under anesthetic, a speedier and more effective recovery, and greater compliance to a rehabilitation regimen. Additionally, the ability for localized manufacturing of the devices has provided patients increased access to the devices, especially in third world countries where receiving shipments of devices can cause a delay in treatment.

Benefits to the Physician

Benefits to the physician for using a patient-matched device include less time in the operating room by removing the intricacies involved in trying to customize a device or surgical instrument to perform within restrictions presented by a patient's anatomy. Physicians also benefit from access to devices created by 3D printing in that they have the ability to use these types of devices even if located in remote areas.

Benefits to the Manufacturer

Benefits to the manufacturer for producing devices created by 3D printing include financial benefits, enhanced productivity, and facilitating access to devices for underserved markets

- Fiscal benefits: Fiscal benefits for the manufacturer of 3D printed medical devices include a reduction in:
    - Costs of storing components – products can be printed on demand without the need for retention of inventory for spare parts and components;
    - Optimized or eliminated supply chain management; the final product can be produced in one process without requiring assembly of several components;
    - Raw material consumption - only the amount and type of material needed is used in the additive creation of the device (i.e., layer-by-layer process) as opposed to traditional manufacturing which uses a subtractive process (it requires more of the material up front and whittles it down to the final finished product); and,
    - Prototyping costs and development time – medical device designers and engineers are able to have a functional or mechanical prototype more quickly than in the traditional process; new designs or adjustments to the medical device can be made and tested quickly.
- Enhanced Productivity: The manufacturer of 3D printed medical devices benefits from increased productivity; these benefits include:
    - Less time spent in prototyping and design development;
    - Products manufactured more quickly – batches of products with differing specifications can be created without having to change, and validate the calibration of that machine; and,
    - Increased opportunities for additional geographical locations for manufacturing.

- Facilitating Access: The representation of physical requirements and specifications due to the digital file allows for global distribution of medical devices; thereby facilitating access to these devices by those who are positioned remotely. This ability and activity increases their commercial geography as well as the positive reception in the global market for their devices.

Regulatory Challenges of Using 3D Printing

Due to the distinctive capabilities of 3D printing there are several regulatory challenges or risks that manufacturers of 3D-printed devices encounter that are not faced by traditional device manufacturers

Design Controls

Customization of 3D printed devices introduces a new complication for manufacturers in drafting a design control plan that will meet FDA's requirements for consideration of clearance or approval of the device made with this technology. Design controls (i.e., a system that evaluates user needs; design inputs, processes, outputs and validation) are required by the FDA for the manufacturing of medical devices; these controls are required at all stages in the development of the device. By establishing a robust design control system, the manufacturer has a structure for identifying potential design flaws, and verification and validation of design performance (e.g., via repeated review of the design).

Build Process

The build processes and customization used in 3D printing present challenges in meeting the quality assurance requirements. A quality build requires quality imaging; conversion of the device file; consistent material (i.e., powder, blood cells, etc.), and optimal printing parameters including the orientation of the build, calibration of the machinery, the power of the laser, the environment of the build site, etc.

- Dependence on the Quality of Imaging: The 3D printing process uses imaging to create devices specifically tailored to a patient's anatomy. Several issues specific to imaging that may affect the fit of the device include:
    - Quality and resolution features of the image – if the images are blurry or not well-defined there could be a problem in the fit of the finished device to the patient;
    - Processing algorithms (e.g., smoothing) could alter the dimensions of the final device affecting the fit of the finished device to the patient; and,
    - The structural features and anatomic landmarks of the anatomy being imaged – for example, if the device is to be tailored for a repair of soft tissue – concerns regarding changes of that soft tissue from the date of imaging until the day of repair could occur due to disease progression or reduced swelling, etc.

- Device File Format Conversions: Measurements of the finished device can be negatively impacted by errors in file conversion. Creating a patient-matched device requires imaging of the patient's anatomy, design manipulation software, and conversion software which creates a

digital file with specifications for the device itself. A challenge inherent in making patient-matched devices is that all of the steps in conversion of the file are performed every time a device is created. In other words, critical attributes of the specific device, and the efficacy criteria of the final device must be validated as part of the software workflow to ensure the performance of the finished device for the individual patient.

- Digital Device Design to Physical Device Considerations: FDA recommends that manufacturers consider additional preparatory processes once the device design is complete. These processes include:
    - Build Volume Placement – the packing density, placement, and orientation of a device within the build volume should be considered as it may be integral to the quality of the device or component.
        - Material properties, surface finish, and ease of post-processing could be affected by the distance between each device or component.
        - Anisotropic properties of the device or component could affect the functional performance of the device depending upon it's build orientation;
    - Addition of Support Material: design features of some devices created by 3D printing may require temporary support structures during the layering/printing process. Removal of the support material can be done either by chemical or physical means. The removal must be conducted carefully to ensure that no surface marks or residues are left behind which may affect the safety and performance of the device.
    - Layer-by-Layer printing (Slicing): Issues occurring during the process of the manufacturing may influence the achievable layer thickness and/or affect the bonding and curing of each layer. Factors that may prove problematic include, but are not limited to:
        - technical characteristics and calibrations of the machine used in manufacturing the device;
        - software capabilities;
        - environmental conditions;
        - physical properties of the material; and
        - power fluctuations occurring amid the layering process.
    - Build Paths: The quality of the finished device may also be affected by the path created by the energy or material delivery system (i.e., extruder or laser). For example, if the device is created with the delivery of material being laid from left to right and then right to left – the material on onside of the component has more time to harden or cool.
    - Machine Calibrations and Parameters – Calibrations of the machinery used in the manufacturing process may affect the finished device especially if they are compounded

or combined (e.g., the speed with which the layers of material in the device is built, the density of the energy used to cure the material, the diameter of the nozzle that lays the material down, etc.).

- Environmental Conditions within the build volume may affect the manufacturing of the device and the properties of it in its final form. For instance, curing between the layers of the AM device may be affected by the atmospheric pressure, humidity, and/or temperature of the room where the manufacturing component is housed.

Due to the factors outlined above that are intrinsic to the 3D printing process, it is essential for manufacturers to have stringent controls in place. Controls needed include machine specifications; software management and protection; environmental conditions of the manufacturing site; and the raw material used in creating the device.

Post-Production

Regulatory concerns exist in post-production of the 3D-printed device, as well. These concerns include cleaning, finishing, and sterilizing processes and establishment of a valid shelf-life for the medical device:

- Removal of Material Residue and/or Effective Sterilization: manufacturers of devices with complex geometries created by 3D printing may have difficulties in removing material residue created by the manufacturing process; and/or in effective sterilization of the device. The challenges experienced are due to the ability of the technology to create devices with tortuous pathways or those with internal voids which have limited or no access to the cleaning and sterilization processes.

- Shelf-life of a Patient-matched device: Standard methods for determining shelf life of a medical device may not be applicable for patient-matched device; the expiration date of a device manufactured by 3D printing may be driven by the imaging date or the design finalization date. Events and/or time from imaging to the completion of the final device may impact its performance. For example, changes in the anatomy of a patient for which the device is designed could occur which could directly impact the dimension requirements and/or the orientation of the device. Note: Current recommendation of FDA is that an additional precaution be added to the labeling of 3D printed devices which would state that a scan for anatomical changes prior to the procedure and placement of the device in the patient is required.

Clinical Data

And, finally, clinical data required by the FDA for clearance or approval of medical devices may be particularly challenging for manufacturers of 3D-printing devices to meet. Manufacturers of devices specifically tailored to meet an individual's anatomical needs (i.e., patient-matched device) are confronted with the task of creating a sufficient volume of customized devices based on specific patient images. Unless 3D printing manufacturers are able to identify clinically relevant design parameters, or a

pre-determined range for these parameters, they may find that supplying clinical data is an insurmountable obstacle.

Summary

Currently, devices created by the 3D process are regulated similarly to devices created through traditional manufacturing methods; however, as the technology advances, manufacturers should expect FDA to update this initial guidance. As mentioned above, existing regulatory requirements for medical device manufacturers may need to be revised to enable the manufacture, and medical use, of 3D printed devices based on the technology of the manufacturing process and the uniqueness of the devices created.