Regulatory Considerations in the Design and Manufacturing of Implantable 3D-Printed Medical Devices

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Abstract

Three-dimensional (3D) printing, or additive manufacturing, technology has rapidly penetrated the medical device industry over the past several years, and innovative groups have harnessed it to create devices with unique composition, structure, and customizability. These distinctive capabilities afforded by 3D printing have introduced new regulatory challenges. The customizability of 3D-printed devices introduces new complexities when drafting a design control model for FDA consideration of market approval. The customizability and unique build processes of 3D-printed medical devices pose unique challenges in meeting regulatory standards related to the manufacturing quality assurance. Consistent material powder properties and optimal printing parameters such as build orientation and laser power must be addressed and communicated to the FDA to ensure a quality build. Postprinting considerations unique to 3D-printed devices, such as cleaning, finishing and sterilization are also discussed. In this manuscript we illustrate how such regulatory hurdles can be navigated by discussing our experience with our group's 3D-printed bioresorbable implantable device. Clin Trans Sci 2015; Volume 8: 594–600

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Introduction

To reach the general market, a medical device must first pass a set of standards and regulations designated by its class.[1]Devices are classified as Class I, II, or III based on risk of the device and the level of control necessary to assure safety and efficacy (*Figure 1A*). Class I devices are considered low-risk and are subjected to general controls alone, while Class III devices, which includes most implants, are considered high-risk and are subjected to the most complete and stringent standards.[2] Class III devices are typically granted an initial Investigational Device Exemption (IDE) allowing use of the device exclusively in a FDA-regulated clinical trial to collect necessary safety and efficacy data prior to market application.[3]

Class III devices can use a number of pathways to reach the market, with the premarket approval (PMA) pathway being most common.[4] A notable alternative mechanism is the Humanitarian Use Device (HUD) program, created for devices intended for patients with rare life-threatening diseases or conditions. Treading through the conventional marketing pathways is a costly process, especially when taking into account the clinical trials run to gather device efficacy data. Consequently, inventors are unlikely to pursue projects that can solve or alleviate rare diseases and conditions since such a solution typically does not translate to a large profit. As a result, the FDA created the HUD pathway to encourage inventors to develop potential devices designed to fight rare diseases. The HUD pathway allows the applicant to develop a medical device without the requirement for efficacy data, and the process is notably expedited, with a decision given to an applicant within 45 calendar days. To acquire HUD designation, the inventor must provide the FDA supporting documentation demonstrating the rarity of a disease, which must affect fewer than 4,000 patients in the United States per year. Additionally, the inventor must include a comprehensive description of the device and its intended use, with scientific rationale behind the device. After the applicant is granted HUD designation and IDE regulations are satisfied, the device is eligible for marketing through the Humanitarian Device Exemption (HDE) pathway, an application similar to the PMA (but much less onerous) in that safety data must be provided, but notably exempt from providing effectiveness data.

Although the FDA readily provides guidance for device regulation, notably through the Pre-Submission Program, it is understandable that regulatory pathways authored to fit medical devices of all kinds are nevertheless complicated to apply, especially with new and rapidly evolving technology such as three-dimensional (3D) printing.[5]

Introduction to 3D printing

Traditional manufacturing, also called subtractive manufacturing, starts with a block of material and removes excess through methods such as milling and machining until a final product is attained.[6] 3D printing, also referred to as additive manufacturing or rapid prototyping, is a process whereby a 3D model of a product is electronically sliced into individual layers and material is deposited in a layer-wise fashion until the final product is built (*Figure 2*). This ability to "build something out of nothing" holds several notable advantages, most notable being the capability to build complex and protean geometries not possible with traditional subtractive manufacturing.[6] 3D printing technology has rapidly penetrated the medical device industry over the past several years, with applications such as patient-specific craniofacial implants for reconstruction of the skull and facial skeleton, titanium hip and mandibular prostheses, and scaffolding for tissue engineering.[7–9] Innovative groups have harnessed the technology to create devices with unique composition, structure, and customizability. However, the unique structures and applications afforded by 3D printing have introduced unique regulatory challenges, which we will illustrate by discussing our experience with our group's 3D-printed bioresorbable implantable device used in treatment of life-threatening disease.[10]

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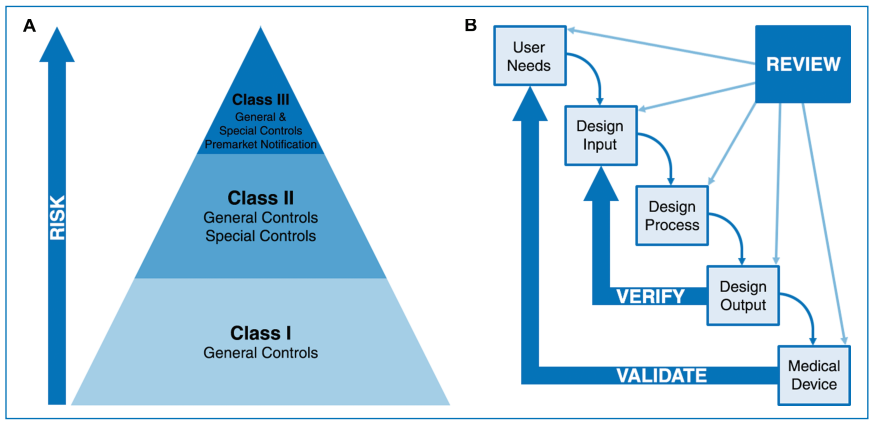

Figure 1. Classification of medical devices and the design control process for device design. (A) Classification of medical devices is based on the degree of risk to the patient. Greater risk necessitates a greater degree of regulatory control for device market approval. (B) The design control model is suggested by the FDA for medical device development. Adapted from U.S. Food and Drug Administration, "Design Control Guidance for Medical Device Manufacturers", Guidance for Industry and Food and Drug Administration Staff, issued March 11, 1997.

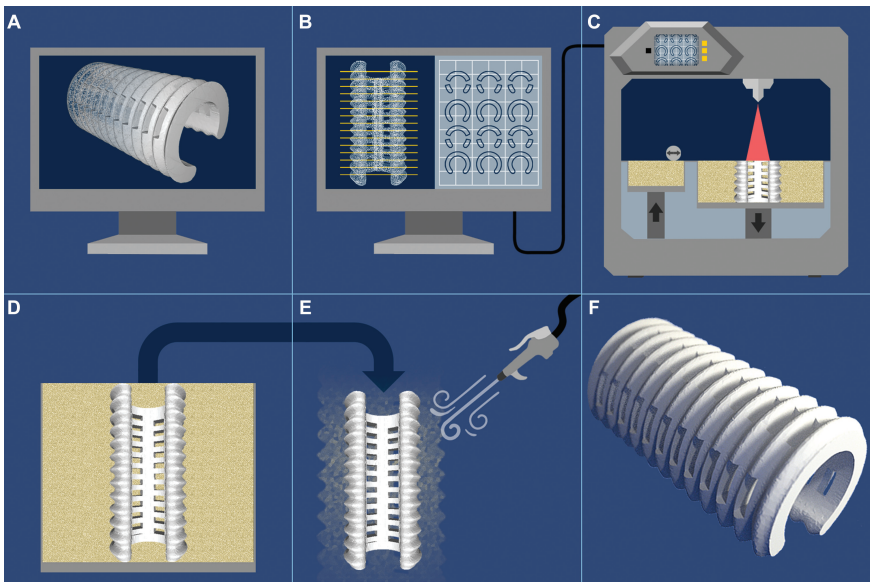

Figure 2. Overview of 3D printing of medical devices. (A) Medical device design is created to user needs with computer-aided design (CAD) software and exported as stereolithography (.STL) file. (B) Device .STL is "sliced" in layer-wise fashion (left) and laid out on virtual build platform (right) using 3D printer software. (C) Build is exported to 3D printer and assembled by depositing material "slice-by-slice" until final model is created. In our process (selective laser sintering), a base substrate powder is spread evenly and a laser melts the powder in the shape of the "slice." The build platform then descends, a new layer of powder is spread, and the next "slice" is melted. (D) For many 3D printing processes, the completed device is buried within a basin of build substrate or powder. The completed device is sifted out of the substrate and extracted. (E) The completed device is then cleaned to remove residual substrate, often by air-jet or waterjet blasting. (F) The final cleaned medical device is then ready for sterilization.

Device Background

Tracheobronchomalacia (TBM) is a pediatric condition of excessive dynamic collapse of the primary airways during respiration. In rare severe cases, standard therapies fail with high rates of treatment-associated and disease-associated morbidity and mortality.[11] Our multidisciplinary team designed an archetype device, termed the tracheobronchial splint (TBS), which uses patient-specific computer-aided design (CAD) to create a custom device to treat this condition.[10] Patient-specific devices are designed by imaging-based CAD and manufactured from a bioresorbable material using a 3D printer (*Figure 3A*). Each device is designed using patient anatomy for design input, a design process which is consistent with the philosophy of personalized medicine and a hallmark feature of 3D-printed medical devices.

As a class III device aimed towards treating a rare disease process, HUD designation with subsequent HDE application was the most appropriate regulatory pathway for the TBS. An HUD application containing a description of the intended use of the device, supporting documentation of the rarity of TBM, and preclinical results was approved in 2012. Our group is currently in the midst of the IDE approval process, with an FDA-regulated clinical trial forthcoming to further define the safety profile of the device.

Preprinting Considerations

Design control

As a requirement for IDE approval, the design control model was implemented in the creation of the TBS. Design control is a system of device development that promotes identification of potential design flaws, creation of multiple design concepts, and verification and validation of design efficacy via repeated design review (*Figure 1B*).[12] The design control model classically consists of the following interrelated categories: user needs, design inputs, design processes, design outputs, and validation (*Table 1*). Though tedious, design control is beneficial as potentially costly design errors are discerned early in the design process.

User needs for the TBS were addressed by Zopf et al., who listed qualitative objectives for an ideal device to treat TBM (*Table 2A*).[13] User needs were subsequently translated into distinct design input requirements (*Table 2B*). In a traditional model, device designs are created to set specifications and a design process is developed to fulfill the specifications. If multiple design variations exist, design processes equal to the number of variants are typically created and validated. Standardizing the design process for 3D-printed devices is uniquely challenging in that these devices allow many design parameters to be customized based on user needs resulting in a potentially infinite number of design variants. As such, it becomes necessary to incorporate design verification and design validation steps into the overall design and manufacturing process for personalized 3D-printed devices.

The TBS includes ten bounded physical parameters utilized as design inputs, each measured to the patient's anatomy (*Table 2B*). This degree of freedom allows over 450 million unique design variations which rendered traditional design process verification

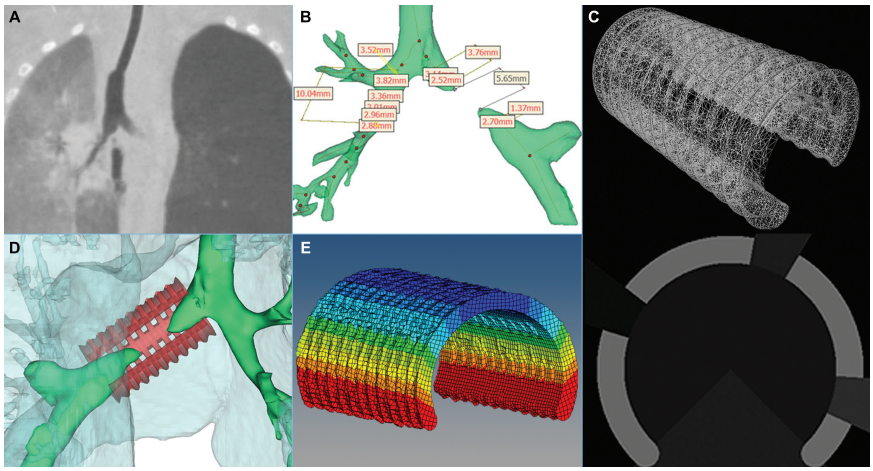

Figure 3. Design process of the tracheobronchial splint. (A) Patients undergo computed tomography (CT) imaging of the airway to characterize the location and severity of disease. (B) DICOM images from the CT scan are used to generate a 3D model of the patient's airway within Mimics (Materialise) on which measurements are performed to generate device design inputs. (C) Design inputs are fed into a proprietary MATLAB (Mathworks) code which generates a series of 2D .TIFF images (representative image left). These are imported into Mimics and used to generate a .STL of the device design (right). (D) Verification of performance requirements is done by virtually fitting the 3D model of the device over the 3D model of the patient's airway to ensure proper fit. (E) Verification of functional requirements is done by converting the .STL of the device into a volumetric mesh and performing finite element analysis (FEA) within ANSYS (Ansys Inc) to ensure proper mechanical behaviors.

impossible, leading us to develop standard operating procedures (SOPs) for our design process. First, we obtain computed tomography (CT) imaging of the patient's airway using fixed, specific imaging parameters. We generate a 3D model of the patient's airway using Mimics (Materialise Inc., Leuven, Belgium) and measure the affected anatomy using MEDCAD functions to generate the ten design inputs. Design inputs are entered into a custom MATLAB (Mathworks Inc., Natick, MA, USA) code that generates the design output as a stereolithography (.STL) file.

Design verification is performed by virtually fitting the generated device model over a 3D model of the patient's airway, to ensure its dimensional properties allow an adequate fit. To date, this process has been sufficient for design verification for the FDA as long as it is performed with each design iteration.

Class III implantable devices typically require both pre-clinical laboratory and animal model testing to validate device performance and establish a safety profile. We developed a porcine animal model of TBM for validation of clinical performance requirements of the TBS.[13] Functional requirements are validated after manufacture via testing of the device on an MTS RT/30 Alliance machine under compression, three-point bending, and open wedge displacement to mimic the *in vivo* environmental forces exerted on the splint.[14] We test each splint design iteration to validate that functional performance fits within the criteria stated within *Table 2A*, as the design output varies with each patient.

Conventional design validation of mechanical performance on the TBS has been cost and labor intensive and is unsustainable when scaling to mass production. Finite element analysis (FEA) is a process by which a virtual mathematical model is created to predict mechanical performance of a virtual model of a device.[15] FEA has been investigated as a surrogate for design validation processes and is in many ways ideally suited for 3D-printed devices as design outputs already exist as a virtual model.[16–18] Additionally, FEA programs can model future states of a device, such as growing tissues or material degradation. For the TBS, an FEA model was designed that simulates a bronchus that grows as the patient ages (*Figure 3B*). Modifications to the model that incorporate material degradation into the model are in development.

FEA is an attractive alternative to conventional mechanical testing as it avoids sacrifice of manufactured devices that conventional testing requires and can be easily applied to a wide variety of design variations. However, FEA models require resource investment for model validation to allow meaningful interpretation of FEA model results.[16–18] Additionally, regulatory approval of FEA as a replacement for conventional design validation of devices has not been explicitly expressed by the FDA. Nevertheless, FEA can be a useful mechanism for assessing device design performance of 3D-printed devices.

Term	Definition
User needs	Qualitative requirements deemed necessary for successful treatment of an illness or condition.
Design input	Requirements of a device that are used as a basis for device design. Typically grouped into functional requirements, performance requirements, and interface requirements.
Functional requirements	What the device does, focusing on the operational capabilities.
Performance requirements	How much or how well the device must perform, addressing issues such as speed, strength, response times, accuracy, limits of operation, etc.
Interface requirements	Characteristics of the device which are critical to compatibility with external systems.
Design process	The process of translating a design concept into a functioning prototype.
Design output	The results of a design effort at each phase of the design process and at the end of the total design effort.
Verification	The process of checking at each stage of the design process whether the design output meets input requirements. If the data from the output is within the acceptable range established by the design input, then the design concept is verified.
Validation	Establishing by objective evidence that final device specifications meet user needs and intended use.

Table 1. Definitions of design control model. Adapted from U.S. Food and Drug Administration, "Design Control Guidance for Medical Device Manufacturers", Guidance for Industry and Food and Drug Administration Staff, Issued March 11, 1997.

A. User needs and requirements for TBS
Clinical user needs
1. Must maintain support for a critical 24-month duration and subsequently degrade. 2. Must predictably and effectively exert a balanced radial force in the axial plane restoring the native lumen size and resisting external compression yet allowing for internal expansion during growth and transverse plane movement during cervical motion. 3. Must be placed external to airway to leave mucociliary architecture unaltered. 4. Must be straightforward to place the device onto the affected airway segment (i.e., low user complexity).
Performance requirements
1. Must be customized to the patient's specific defect size and location to 0.5 mm accuracy.
Functional requirements
1. Must exhibit maximum displacement of less than 10% of initial splint diameter under 50N compressive load. 2. Must exhibit displacement greater than 20% of initial splint diameter, but less than 50% of initial splint diameter under 50N three-point bending load. 3. Must exhibit a displacement greater than 20% of initial splint diameter under 15N opening angle load.
Biomaterial requirements
1. Must not cause tissue reaction or remodeling (i.e. non-erosive), local or systemic toxicity. 2. Must exhibit a degradation profile which ensures structural integrity for a critical 24-month duration and be fully bioresorbable.
B. Design process for TBS
Generating design inputs
1. Thin-cut computed tomography (CT) images of patient's airway are obtained in inspiration and expiration. 2. DICOM images of CT scan are input into Mimics and used to generate 3D model of patient's airway using threshold function. 3. Centerline function is performed on airway model, and measurements performed to generate TBS design inputs. 4. Design inputs: X diameter, Y diameter, wall thickness, bellow height, bellow wave shape, bellow periodicity, suture hole thickness, open wedge angle, length, spiral to open wedge angle.
Design process
1. Design inputs are fed into proprietary MATLAB code which generates series of 2D .TIFF slices. 2. TIFF slices input into Mimics to generate 3D model (.STL) of TBS design.
Design output verification
1. 3D model of TBS virtually fit over 3D model of patient's airway to ensure proper fit within Mimics. 2. Finite Element Analysis (FEA) of design output in compression, three-point bending, and open angle displacement meets user needs criteria.
C. Device validation for TBS
Clinical validation
1. Manufactured device based on design output alleviates symptoms of TBM in preclinical animal model. 2. Manufactured device based on design output does not demonstrate airway growth restriction in preclinical animal model.
Mechanical validation
1. Bench mechanical testing of manufactured device based on design output in compression, three-point bending, and open angle displacement meets user needs criteria.
Biomaterial validation
1. Device manufacture material composition meets ISO 10993 standards. 2. Manufactured device based produces no adverse tissue reaction in preclinical animal model.

Table 2. Design control process for the 3D-printed tracheobronchial splint.

Printing Considerations

Raw materials

FDA Quality System (QS) Regulation/Medical Device Good Manufacturing Practices for industry manufactured devices should be implemented throughout the manufacturing process of 3D-printed implantable devices, beginning with the substrate used for manufacture.[19] Source materials for 3D printing should be evaluated as they are for any other manufacturing process, with appropriate quality control to ensure homogeneous and traceable manufacturing substrate.

For our device, we use a mix of 95% polycaprolactone (PCL) with 5% hydroxyapatite (HA). PCL was utilized as our manufacturing substrate due to its biocompatibility and bioresorbability profile, while HA was added as a flowing agent to improve powder distribution during printing. Virgin PCL powder is cryogenically milled to a median particle size of 40–60 μm, promoting a higher resolution build with more accurate physical dimensions and uniform density.[20] To ensure regulatory quality requirements, the powder is tested after milling using standardized procedures to ensure a uniform particle size and polydispersity index. These procedures were deemed appropriate by the FDA.

While many of the Quality Assurance (QA) processes for 3D-printed devices are identical to those that have been used in industry for decades, a unique manufacturing process allowable by 3D printing is "recycling" of manufacturing substrate from one build to the next. It has been previously demonstrated that

Device categorization by		Biologic effect							
Nature of body contact	Contact duration A – limited (<24 h) B – prolonged (>24 h to 30 d) C – permanent (>30 d)	Cytotoxicity	Sensitization	Intracutaneous reactivity	Systemic toxicity (acute)	Subchronic toxicity (subacute)	Genotoxicity	Implantation	Hemocompatability
Tissue / bone	A	X	X	X	O				
	B	X	X	X	X	X	X	X	
	C	X	X	X	X	X	X	X	
Blood	A	X	X	X	X	X		X	X
	B	X	X	X	X	X	X	X	X
	C	X	X	X	X	X	X	X	X

Table 3. FDA recommended initial ISO 10993 evaluation tests for implant devices; X = evaluation tests for consideration; O = additional evaluation tests should be addressed in the submission, either by inclusion of the testing or a rationale for its omission. Note: Tissue includes tissue fluids and subcutaneous space. Adapted from US Department of Health and Human Services, "Use of International Standard ISO-10993, Biological Evaluation of Medical Devices Part 1: Evaluation and Testing. Draft Guidance for Industry and Food and Drug Administration Staff", Draft Guidance, Issued April 23, 2013.

for many 3D printing processes, the use of recycled substrate may result in superior quality of manufactured devices.[21,22] However, there have been concerns expressed by the FDA and others that recycling introduces potential for material contamination, diminishing performance of recycled materials over time, and additional complexities with material traceability. Several methods have been proposed method to mitigate these issues, including use of defined refresh rate of recycled-to-virgin powder with a controlled number of allowed cycles and a set expiration date or routine retesting of recycled materials.[21,23] It is yet to be determined whether routine recycling of materials for 3D-printed implantable devices will be acceptable by the FDA. Further work to define the potential for material contamination and further shelf life testing of 3D printing biomaterials are necessary to better characterize these risks, and in-depth study of the chosen raw materials will be necessary for regulatory approval of 3D-printed implants.

Technical considerations

A number of 3D printing parameters have been shown to significantly impact the physical characteristics of the final manufactured device, such as laser beam energy density, scanning speed, deposition velocity, and humidity within the build environment.[1] As such, quality measures to ensure consistency between builds are needed and necessary to document for regulatory purposes.

Previous work has demonstrated that 3D-printed devices can have only 15% tensile strength in the build direction, especially in laser sinter systems.[24,25] This is thought to be due to anisotropy introduced between print layers and is especially applicable to devices with complex structures or devices used in load-bearing regions of the body. Additionally, in certain 3D printing processes the position of the device layout within the build platform can result in device variations.[23,26] Much like a batch of cookies baking in an oven, "hot spots" and "cold spots" exist and devices built in unfavorable positions such as the platform edges are at increased risk of warping. Characterization of the mechanical properties of the device along specific z-axis orientations and characterization of the build platform environment with standardized constructs (informally referred to as "coupons"), as described by Jande et al., have been proposed as a mechanism to test consistency of 3D printing builds.[27]

To decrease the risk of build inaccuracies, the FDA will require that all printing parameters and processes for the TBS be included in the IDE application. We developed a fixed range of build parameters for the TBS to ensure consistency of laser sintering of PCL based on prior work by our group. These include laser power of 4 Watts, bed temperature of 50–56°C, laser scanning speed of 1000–1500 mm/sec, and scan spacing of 0.15-0.20 mm.[28–32] The optimal orientation (longitudinal along the z-axis) and position on the build platform were determined with mechanical testing and standardized for the IDE application so that the z-axis is orientated along the length of the device. Additionally, as recommended by Jande et al, standardized porous cylindrical constructs are manufactured and tested as coupons with each build to detect any significant build variations.

Postmanufacture quality assurance

Despite appropriate quality controls for printing processes, variations in manufactured devices may still occur. There have been a variety of techniques employed by various authors to ensure the final product is representative of the design output. These include surface laser scanning, micro-CT and various printer monitoring strategies.[33] The specific techniques chosen for postmanufacture quality assurance testing are often determined by the material utilized and the size and shape of the device. For devices with complex internal structures, postmanufacture device "cutups" may be required to assess the fidelity of the entire manufactured device. As of yet, standard guidance for post-manufacture QA of 3D-printed devices has not been published. For the TBS, we utilize caliper measurements of wall thickness, inner diameter, and length, and are currently implementing micro-CT processes to assess device geometry and density. These processes were deemed sufficient by the FDA for the IDE application.

Postprinting Considerations

Cleaning and finishing

Cleaning of postmanufacture 3D-printed devices is necessary regardless of the 3D printing technique used. The method of cleaning varies based on the printing process utilized, from removal of support material to removal of residual monomers. Certain techniques may require additional finishing processes such as tumblers or sandblasting. Extraction of residual material by the cleaning process should be complete, which may be difficult in 3D-printed devices that employ porous surfaces or complex internal structures. This is of particular relevance if support materials or flowing agents are not biocompatible, and may present a hurdle to regulatory approval if cleaning processes cannot be demonstrated to be sufficient.

Validation that finishing processes do not alter the overall structure or mechanical properties of the manufactured device beyond design input requirements will likely be necessary, but has not been explicitly expressed by the FDA to date.[34] This is of particular concern given that microporosity from the printing process may serve as critical crack initiation sites if finishing processes are too aggressive. Validation of device geometry and mechanical performances postfinishing processes can serve as a mechanism to overcome this regulatory barrier.

In our laser-sintering process, devices are cleaned via air-blasting in a contained environment to remove gross excess powder, followed by sonication in ethanol to remove residual debris. All devices were mechanically tested after cleaning to ensure the cleaning process did not significantly alter device functional performance, and this was deemed appropriate for incorporation in the IDE application. We do not employ any finishing techniques and as such did not have to validate device postfinishing processes.

Biocompatibility

The International Organization of Standards (ISO) has published a set of standards for evaluating the biocompatibility of materials used in the manufacture of medical devices, collectively termed ISO 10993.[35] The FDA has adopted these standards and enforces them for Class III devices.[36] The device structure, material composition, and intended use ultimately determine which aspects of ISO 10993 are necessary for regulatory approval (*Table 3*).

Unique factors arise when attempting to apply these standards to 3D-printed implants. Raw materials may be altered by the 3D printing process (such as cross-linking or melting) which can potentially alter the material's properties. [37] As such, testing of raw materials may be insufficient. Additives during the manufacturing process (such as support materials, flowing agents, or binding materials) may also need to be tested sure ensure they are removed completely during cleaning processes or that they are ISO 10993 compliant if still present within the final manufactured device. For biodegradable implants, it is important to fully characterize the degradation profile using *in vitro* and *in vivo* degradation studies. Degradation testing may also be necessary for shelf life testing of final manufactured devices.

For the TBS, the FDA recommended that degradation testing be performed on bounded extremes of the device design inputs, incorporating the largest and smallest potential devices. This narrowed our design variations to be tested from greater than 64 million to 115. Accelerated *in vitro* degradation testing, where devices were submerged in a basic solution in an incubator, was explicitly requested by the FDA to characterize the mechanical performance of the TBS over 9 months. This time frame mimicked the time-critical period the device must be intact for treating tracheobronchomalacia.Real-time *in vivo* degradation testing and stress testing of bounded device designs of up to 36 months was requested to be run concurrent with the clinical trial.

Sterilization

Sterility is fundamental to minimizing risk of infection with implantable medical devices. Given the numerous materials utilized in 3D printing, a variety of sterilization processes can potentially be employed. The sterilization process may be determined by device-structure, compatibility between the process and device material, or process availability. Sterility assurance level (SAL) is the probability of a single unit being nonsterile after it has been subjected to sterilization. Material compatibilities may require deviation from standardized sterilization protocols, which makes validation of SAL essential. For example, the melting point of PCL is 60°C, which lies below the standard temperature for most conventional sterilization processes, including steam sterilization and ethylene oxide (EtO) gas sterilization. We utilized a modified EtO gas sterilization protocol for sterilization of the TBS with a lower gas temperature (49°C).

Regardless of the sterilization process, 3D-printed implants require the same validation of SAL as any other medical implant and results must be presented to the FDA as part of the marketing application.[37] The battery of validation tests required depends on the materials used and the sterilization method, and will likely require consultation from the FDA on a case-by-case basis. Classic sterility validation requires all design iterations of a device to undergo validation testing. Similar to device design validation, sterility validation of 3D-printed implants is not feasible given the infinite potential design variations. The FDA requested that sterility validation be performed on bounded design variables of the TBS in a similar model to degradation testing. Additionally, the FDA requested that minimal requirements to demonstrate device safety performed, which for the TBS included *in vitro* cytotoxicity studies under ISO 10993–5 requirements. Validation will be performed using a battery of testing, including biologic indicator testing, pyrogenicity and endotoxin testing, and residual EtO gas testing. The FDA also stated that they will consider sterilization from previously implanted patients. Further input from the FDA will be required to develop consensus strategies for sterility validation of 3D-printed medical devices that are highly variable in structure.

Conclusions

The expansion of 3D printing technology has produced innovative medical devices with novel composition and structure. The ability to rapidly alter size and shape of these devices to meet specific patient needs allows for rapidly producible "custom" devices but introduces unique regulatory challenges for device design development, manufacturing, biocompatibility, and sterilization. Applying the same design and quality control strategies utilized in standard manufacturing methods with 3D printing will result in a controlled output and consistent production of devices. However, given the "custom" nature of many 3D-printed implants, further guidance is necessary to establish which quality control measures will necessary for each device iteration. The maturation of 3D printing within the biomedical industry will ultimately be dependent on the ongoing evolution and synthesis of regulation and technology.

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Competing Interests

Authors S.J.H. and G.E.G. have filed a patent application related to the device. The authors declare no other competing financial interests.

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