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3-D Printing

Pathways to FDA Approval for 3-D Printed Medical Devices

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3-D printing technology is being used to create orthopedic implants, dental constructs, and a host of other medical devices. William J. Cass of Cantor Colburn breaks down the processes by which companies can apply for and gain Food and Drug Administration approval of their 3-D printed devices.

BY WILLIAM J. CASS, ESQ.

3-D printed medical devices are gaining approval at the Food and Drug Administration (FDA). This is not surprising, given that many of the same materials used in 3-D printing have been used in medical products for decades. The approval process and expenses in bringing the device to market, however, differ significantly depending on whether the device qualifies for the abbreviated approval process—known as a premarket notification (under 510(k))—because the device is substantially equivalent to a legally marketed device, or whether the device must be fully vetted under the FDA premarket approval process.

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3-D printing, also known as additive manufacturing, allows components to be made layer by layer. Layered manufacturing, in combination with computer-aided design (CAD), allows products to be individually tailored to the patient and constructed in geometries that take advantage of this process. The early technologies of the 1980's, based on fused deposition modeling, in which an object was constructed in layers of heated plastic, and stereolithography, in which the plastic layer of the object was cured by ultraviolet light, have also led to the production of high quality metal components. These metal components are constructed by fusing layers of metal powder, in a process known as powder bed fusion. Each layer of powdered metal is sequentially fused to build the object. More powerful techniques, such as electron beam sintering, afford parts that are incredibly strong. The end result is that a host of medical devices, such as bone implants, fixation devices, cranial implants, and teeth, are suitable for use in the human body and are constructed out of both plastic and metals. Importantly, the processes used to develop these devices now provide the consistency necessary to establish process validation, quality control, biocompatibility, and associated testing for approval as an accepted medical device.

3-D printed body tissues, which can form an implantable device, are also just over the horizon. The 3-D printed body tissue is constructed in layers by using a

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scaffold or base, which can also be 3-D printed, made of a bio-compatible polymer or naturally occurring material. The living tissue is then added layer by layer (or injected) to generate the body part. The complexities of printing bio tissues are many. Metals and plastics can be subjected to high pressures and temperatures. Biotissues, however, must be delivered so that the tissue isn't destroyed, and at temperatures and pressures which allow the tissue to generate. Further techniques are necessary once the tissue is in place, such as vascularization to deliver oxygen and nutrients. Thus, getting the cellular matrix into position is only one of the many unique problems associated with the storage, delivery, application, and construction of bio-tissues. Wake Forest University, for example, has famously printed an ear and holds several patents on its technology. Research in this field is being conducted throughout the world. However, the pathway to regulatory approval for this technology will be complex due to the innovative nature of the construction of these devices and its cellular construction. There is no substantial equivalent to a legally marketed device to allow for the abbreviated approval process. Therefore, the premarket approval process applies.

Premarket Notification

Navigating the approval process through the FDA, while complicated, follows a fairly defined regulatory course. The easiest and most common pathway toward regulatory approval comes under the premarket notification procedure provided under Section 510(k) of the Medical Device Amendments of 1976 to the Federal Food, Drug, and Cosmetic Act. A 510(k) is a submission made to the FDA to demonstrate that the device to be marketed is as safe and effective as, that is, substantially equivalent to, a legally marketed device that isn't subject to premarket approval. A 510(k) (premarket notification) to the FDA is required at least 90 days before marketing unless the device is exempt from 510(k) requirements. This shortened approval process was created to streamline the approval process of new devices.

On May 10, 2016, the FDA issued a draft guidance document entitled *Technical Considerations for Additive Manufactured Devices*. Guidance documents aren't regulations but publications for FDA staff, regulated industry, and the public that describe the FDA's interpretation and/or policy. This particular guidance document was described by the FDA as a *leap frog* guidance document, meant to share the FDA's initial thoughts on this emerging technology. For the public, this is excellent news, as the FDA both recognized the value of additive manufacturing early on and has been proactive with the public, industry, and staff in providing guidance.

Many devices constructed with additive manufacturing are constructed of similar materials to previously approved devices. Their use, toxicity, strength, and other parameters are known and accepted. As a recent example, on August 11, Renovis Surgical Technologies, Inc. announced it had received a 510(k) clearance from the FDA to market its additive manufactured posterior lumbar Tesera porous titanium interbody fusion systems. Titanium has long been an accepted material for the construction of implants. Interbody fusion systems are known. Thus, approval is gained by establishing that the device is substantially equivalent to a legally marketed device, even though produced by a new method. Presumably, the applicant established consistency in process validation, quality control, biocompatibility, and associated testing to gain approval for production with 3-D printing. Such approvals are occurring for cranial implants, dental constructs, bone implants, and a host of other devices.

A device constructed of 3-D printed body tissues, however, is an example of a new device that for the most part doesn't have a substantial equivalent to a legally marketed device. Thus, the pre-market notification procedure under 510(k) is inapplicable. This distinction means that the pre-market approval process must be undertaken. Additionally, human cells or tissue intended for implantation, transplantation, infusion, or transfer into a human recipient is regulated as a human cell, tissue, and cellular and tissue-based product, or HCT/P. The Center for Biologics Evaluation and Research of the FDA regulates HCT/Ps under 21 CFR Parts 1270 and 1271.

Premarket Approval

To gain premarket approval, the FDA requires technical information to properly evaluate the application, including non-clinical laboratory studies and clinical investigations. The non-clinical laboratory studies section includes information on microbiology, toxicology, immunology, biocompatibility, stress, wear, shelf life, and other laboratory or animal tests. Further, non-clinical studies for safety evaluation must be conducted in compliance with 21 CFR Part 58 (Good Laboratory Practice for Nonclinical Laboratory Studies). The clinical investigations section includes study protocols, safety and effectiveness data, adverse reactions and complications, device failures and replacements, patient information, patient complaints, tabulations of data from all individual subjects, results of statistical analyses, and any other information from the clinical investigations. The bottom line for premarket approval of a new device/therapy is that the approval process is very expensive, time consuming, and a lengthy process.

There are several exemptions to the premarket approval process. According to the FDA, an Investigational Device Exemptions (IDE) allows an investigational device to be used in a clinical study to collect the safety and effectiveness data required for a premarket approval application or a premarket notification (510(k)) submission to the FDA. Clinical studies with devices of significant risk must be approved by both the FDA and an Institutional Review Board (IRB) before the study can begin. Studies with devices posing nonsignificant risk must be approved by an IRB before the study can begin. The FDA observes a 30-day review period for IDE applications. The agency focuses its review on the data provided to demonstrate the safety and anticipated benefits of the device for use in humans, as well as the scientific validity of the proposed clinical trial protocol. After the clinical trials the investigational device can achieve approval through the premarket approval process (and in some cases premarket notification).

There is also a Humanitarian Device Exemption (HDE). A humanitarian use device (HUD) is a device that is intended to benefit patients by treating or diagnosing a disease or condition that affects fewer than 4,000 individuals in the U.S. per year. HUDs are exempt from requirements to demonstrate effectiveness. The

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device must be used at a facility with an IRB. Examples of HUDs include a fetal bladder stent, iris replacement, radioactive microspheres for cancer treatment, and semi-constructed finger joints.

There are many processes associated with additive manufacturing that can impact product consistency, strength, and quality. Material deposition rates, layer thicknesses, processing parameters such as heat and pressure, speed of application, tempering, coatings, and the like, can lead to varying results. Much of the promise in recent years for this technology has been the ability to achieve consistent results. The FDA guidance document outlines the steps necessary to establish the efficacy, quality, consistency, and documentation necessary for approval.