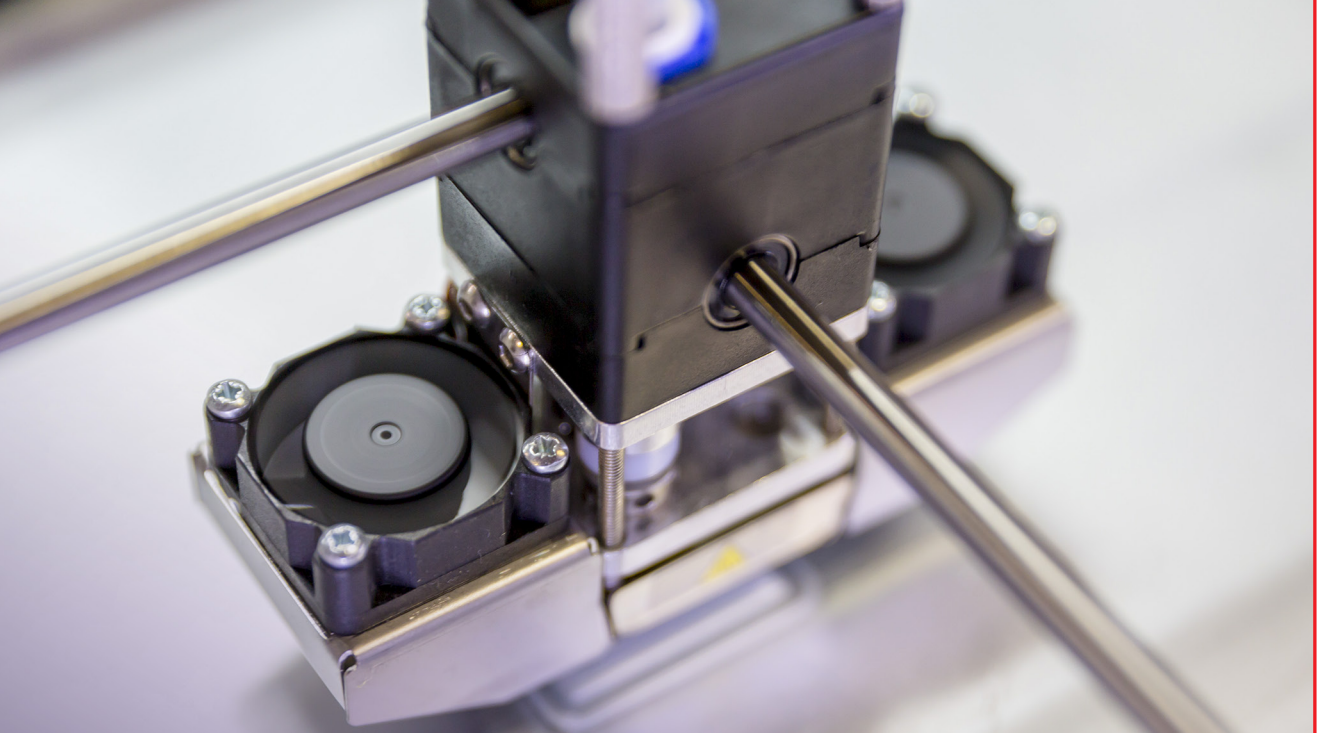

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Three-Dimensional Printing: Key Regulatory and Risk Issues

Three-dimensional (3D) printing is a computerized, additive manufacturing process in which successive layers of material are deposited until a solid object is created. Although it has been in existence in some form for more than three decades, its rapid growth in recent years has resulted in a spate of media attention.

According to reports, the healthcare applications of 3D printing range from novel pharmaceutical drug products to "bioprinted" organs to medical device innovations. As of February 2015, the U.S. Food and Drug Administration (FDA) had already approved approximately 85 3D-produced devices. According to Stephen Pollack, Director, FDA Office of Science and Engineering Laboratories, the FDA views additive manufacturing as an "enabling technology," similar to computer numeric control machining, adding that "it's not something we're unprepared for with the current paradigm we have for regulation."[1]

But questions have been raised about how the technology may affect medical device quality, and departments within the FDA are investigating such questions as the impact of printing materials on strength and durability, as well as design tolerances and their affect on patient safety.[2]

This edition of *Life Sciences POV®* examines the question of how 3D printing fits into the FDA regulatory regime. It also discusses other concerns including whether the advent of this "on-site" technology will lead to hospitals and other healthcare facilities being viewed and regulated as manufacturers, which has product liability implications in the hospital setting.

BASIC REGULATORY PATHWAYS

While a medical device manufacturer may employ several regulatory pathways during the FDA review process, the two primary review standards are based on the 510(k) or Premarket Approval (PMA) processes. Both routes ultimately involve principles of safety and effectiveness.[3] (21 CFR §§807 and 860.) However, under the 510(k) standard, the FDA analysis focuses on the *substantial equivalence* of the new device compared with an existing, legally marketed "predicate" device.[4] The PMA review, on the other hand, requires the applicant to *independently* demonstrate, using scientific evidence, the safety and effectiveness of the device for its intended use.[5]

1 Hartford, J. "FDA's View on 3D Printing Medical Devices," *Medical Device and Diagnostic Industry News*, February 11, 2015.
2 Gaffney, A. "FDA Plans Meeting to Explore Regulation, Medical Uses of 3D Printing Technology," *Regulatory Focus*, May 16, 2014.

3 "The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications" ("Guidance document"), page 6. Guidance for Industry and Food and Drug Administration Staff, issued July 28, 2014. Also see 21 USC §360c, under which the safety and effectiveness of a device are to be determined:
(A) with respect to the persons for whose use the device is represented or intended,
(B) with respect to the conditions of use prescribed, recommended, or suggested in the labeling of the device, and
(C) weighing any probable benefit to health from the use of the device against any probable risk of injury or illness from such use.
4 21 CFR §807.92(a)(3).
5 21 CFR §814.20(b)(3)(vi).

The 510(k) clearance pathway is highly preferable, as it avoids the cost, time and risk of human testing. In fact, over 97 percent of devices registered today with the FDA are cleared through the 510(k) premarket notification (PMN) clearance or are exempted from it outright.[6] This article focuses on the regulatory and liability considerations specific to 3D-printed medical devices.

SUBSTANTIAL EQUIVALENCE

According to Section 360c(i)(1)(A) of the Federal, Food, Drug and Cosmetic (FFD&C) Act, 21 U.S.C. Chapter 9, for a new product to be deemed substantially equivalent to a predicate device, it must have the same *intended use* and *technological characteristics* as the predicate device. If the device has different technological characteristics, it may still be considered substantially equivalent if these variances *do not raise different questions of safety and effectiveness*.

The manufacturer must first identify the legally marketed device (i.e., the predicate device) to which the new device under PMN review is evaluated. FDA then compares the devices based on these three concepts, which are integral to the substantial equivalence analysis and so deserve closer scrutiny.

Intended use. The analysis begins by determining whether the two devices have the same intended use, i.e., the same general purpose and function.[7] This determination can be demonstrated by proposed labeling and related advertising claims. An example of label claims with the same intended use would be "a mechanical device intended for embryo dissection" and "an electronic device intended for embryo dissection."[8] Once the FDA determines that there is a valid predicate device with the same intended use, the following additional factors will be assessed to determine substantial equivalence.

Same technological characteristics. Technological characteristics include the "materials, design, energy source, or other features of the device."[9] The FDA compares these features of the devices and determines if they are the same. If they are not the same, the FDA reviews the performance data to ascertain whether different questions of safety and effectiveness are raised at this decision point. This concept is discussed on page 3 in greater detail.

The FDA Guidance document notes the types of technological characteristics that must be described, when applicable, in the submission:

- *Materials*: Even though FDA does not clear/approve device materials, a detailed chemical formulation of construction materials should be provided especially for materials that come into contact with the patient. The manufacturer also should identify the additives, such as colors, coatings and other surface modifications; the type of processing undergone by the material (e.g., forged versus cast metal); and the state of the material (e.g., amorphous versus crystalline), all of which may significantly contribute to the safety or affect the functioning of the device.
- *Device design*: The description of the device should include engineering drawings or other figures; a diagram for multiple-component devices showing how different elements work together; and a discussion of the physical specifications, dimensions and design tolerances that are critical to the new device.
- *Energy sources*: This characteristic includes both how the device is powered (e.g., by batteries) as well as any type of intentional energy delivery (e.g., laser, radiofrequency, ultrasound, etc.) that affects the patient and/or the healthcare professional using the device.
- *Other key technological features*: Examples include software/hardware features, density, porosity (see page 20 of the FDA Guidance document), degradation characteristics, etc., which are not characteristic of the materials, design or energy source.

The applicant should present the technological characteristics in a tabular form for FDA review. And while performance data are not required when the technological characteristics are the same, it is advisable to include this information in some form.[10] As discussed below, differences in technological characteristics will dictate the scope and degree of performance data requested by the FDA.

6 Calculation based on a product code description for a given premarket submission number. Thus, while duplicate product codes for a unique manufacturer/owner were factored into the calculation, one code may represent multiple like-devices with different proprietary names.

7 21 CFR §801.4 states, in part, "[t]he words *intended uses* or words of similar import … refer to the objective intent of the persons legally responsible for the labeling of devices. The intent is determined by such persons' expressions or may be shown by the circumstances surrounding the distribution of the article. This objective intent may, for example, be shown by labeling claims, advertising matter, or oral or written statements by such persons or their representatives … ."

8 This example highlights the same intended use criterion but would not likely satisfy the other substantial equivalent criteria. Also see pages 16-18 of the FDA Guidance document for an explanation of the relationship between indications for use and intended use.

9 21 §360c(i)(1)(B) and 21 CFR §807.100(b)(2)(ii)(A).

10 From page 22 of the FDA Guidance document: "Very few 510(k) submissions rely solely on descriptive information about materials, design, specifications, and other technological characteristics."

Different questions of safety and effectiveness. Although the technological characteristics of the comparison devices may differ, the devices could still be considered substantially equivalent if they do not raise a different question of safety and effectiveness. However, if different *types* of safety and effectiveness issues are identified in the new device that are not applicable to the predicate device, then the device will be considered not substantially equivalent. Therefore, the 510(k) clearance route would not be appropriate. But if the different technological characteristics do *not* raise different questions of safety and effectiveness, then the performance data will be evaluated by FDA to support a determination of substantial equivalence.

In assessing engineering performance data, the FDA may examine a wide range of factors, including "fatigue, wear, tensile strength, compression, flowrate, burst pressure; electromagnetic compatibility; sterility; stability/shelf life; software validation; and other forms of non-clinical [testing], including device-specific."[11] Often, "other forms of non-clinical" data are generated from animal and/or biocompatibility testing.

Not all medical devices produced by 3D printing technologies present the same clinical or manufacturing risks. For example, whether devices are load-bearing, implantable, or patient-matched rather than standard-sized, will affect the scope and depth of performance data needed to make a determination of substantial equivalence.[12] It should be noted that the FDA considers the potentially burdensome nature of demonstrating substantial equivalence and requests information accordingly.[13]

One of the major issues surrounding 3D printing of medical devices is whether the FDA will regulate hospitals as manufacturers and whether the printer or end product will be regulated.

LIABILITY QUESTIONS AND CONCERNS

As previously noted, many medical devices have already been produced by additive manufacturing techniques.[14] However, legal, risk, and regulatory questions and concerns about the process remain.

One of the major issues surrounding 3D printing of medical devices is whether the FDA will regulate hospitals as *manufacturers* and whether the printer or end product will be regulated.[15] According to the FDA Regulations, a manufacturer "means any person who designs, manufactures, fabricates, assembles, or processes a finished device."[16] Thus, according to this definition, a hospital or similar user facility would qualify as a manufacturer if it were to "print" a medical device.

The concerns raised about this possibility may be exaggerated. Whether it would be more efficient, cost-effective or clinically beneficial to print/manufacture at the hospital is questionable. Today, a healthcare professional can scan an anatomical structure and send the image to the original equipment manufacturer (OEM), which would produce the device and deliver it to the hospital. There may be emergency scenarios where even a same-day courier would not be able to deliver the device on time, but such situations seem exceptional. In general, an OEM would presumably produce devices more quickly and efficiently than a hospital with any time savings probably outweighed by the OEM's production expertise.

Currently, hospitals and research institutions can produce (i.e., "manufacture") medical devices that are being investigated under an investigational device exemption (IDE) and/or through an emergency use authorization. The FDA regulates these operations differently than it does third-party or OEM manufacturing providing *finished* medical devices.[17] However, 3D or additive printing still falls within the parameters of a manufacturing process. Simply because a device can be produced internally does not necessarily mean it exists outside the purview of the Regulations whether it is for investigational use or if it is a finished device.[18]

11 Page 22 of FDA Guidance document.
12 Page 82, Food And Drug Administration (FDA) Public Workshop Additive Manufacturing Of Medical Devices: An Interactive Discussion On Medical Considerations of 3D Printing, October 8, 2014. ("10/8/14 Workshop").
13 21 USC §360c(i)(1)(D).
14 See the Hartford article previously cited and Reed Smith LLP, "3D Printing of Medical Devices: When a Novel Technology Meets Traditional Legal Principles," September 9, 2015, page 10. The table here summarizes some of these approved devices.
15 See the Reed Smith article and the Gaffney article, both cited previously, as well as Brexis, "Some Ideas About 3D Printing", *Drug and Device Law*, posted February 5, 2015.
16 21 CFR §820.3(o).
17 Investigational devices are not subject to the full scope of 21 CFR 820 with the exception of 21 CFR §820.30.
18 See 21 CFR §§812 and 820. See also §§11 and 801, 803, 806, 807, 814, and 821.

While circumstances may be envisioned where on-site manufacturing of a medical device may be desirable, this stage may not be imminent. One of the commonly cited benefits of 3D-printed devices is customization, whereby the product would be printed to match the exact dimensions of the patient's anatomy. However, under both 510(k) and PMA, the FDA reviews, clears and approves many patient-specific medical devices that require final manufacturing once a patient's physical dimensions are measured and sent to the OEM for finishing.[19] These "envelope" submissions, where the range of specifications has been cleared previously or studied clinically, permit some scope of customization. The current regulatory system also has provisions for devices that require variety in their specifications.[20]

Aside from the technical feasibility or clinical benefits derived from on-site 3D device production, if these capabilities were such that a hospital employee could push a button on a printer equipped with the OEM's approved design, method and software system to generate a device, and follow the OEM's instructions for use, then one could argue for a regulatory change that would exempt hospitals from being deemed manufacturers. Without an exemption, it appears the FDA would view the hospital as a manufacturer and thus it would bear any corresponding regulatory responsibilities. Consequently, hospitals may not be an enthusiastic buyer after weighing these considerations. Moreover, regardless of the manufacturing status of the hospital, under the current system, OEMs endeavoring to market such a system (i.e., the "device"), whereby the end-user can print and produce a finished device, would likely have to undergo the IDE/PMA process and prove, among other things, that the "manufacturing" process produces safe and effective devices by the end-user.

While it may not be an appealing prospect for the hospital to assume the responsibilities associated with current good manufacturing practices (cGMP) (unless on-site manufacturing offers significant benefits), it is worth noting that FDA oversight and inspections of hospitals and research centers is not a foreign concept. In fact, the FDA regulates and/or inspects a range of activities occurring at hospitals and research centers.[21]

SERVICES VERSUS MANUFACTURING

If an OEM device manufacturer demonstrated its "one-touch system" produced a safe and effective finished medical device, then the hospital/user facility employing that system may occupy the *services* end of the liability spectrum rather than the *manufacturing* end. Arguably, if such a system had the requisite regulatory approval, it would not differ from the preparation process required by other commercial medical devices (e.g., instructions describing how to prepare a device before use). Thus, the pre-printing, printing and post-printing considerations and processes would be evaluated as a whole based upon PMA requirements (21 CFR §814).

In such a case, fully or partly exempting the hospital or other user facility from 21 CFR §820 could make sense from a commercial perspective by signaling to OEMs that there may be a wider market for 3D printing production systems for qualified devices if hospitals were exempt from manufacturing regulations. And knowing that such an exemption exists before engaging in costly and/or risky trials could be helpful for OEMs developing a medical device production system. As a result, the printing of the item becomes, arguably, merely one step in the product's preparation and is comparable to providing instructions on how to prepare a medical device before it is used.[22] Under these hypothetical circumstances, the user facility may print the device onsite free from additional cGMP regulations.

If an OEM device manufacturer demonstrated its "one-touch system" produced a safe and effective finished medical device, then the hospital/user facility employing that system may occupy the services end of the liability spectrum rather than the manufacturing end.

19 See "Custom Device Exemption, Guidance for Industry and Food and Drug Administration Staff," page 6.

20 Note that, according to 21 USC §360j(b), devices that must be customized to a patient's anatomy are not considered custom devices within the meaning of the FD&C Act's "custom device exemption" unless they comply with all of the criteria specified in §360j(b).

21 Regulated activities include institutional review boards and clinical investigators; cellular, tissue, and gene therapy production; and blood and tissue compliance.

22 See the FDA's "Guidance on Medical Device Patient Labeling" and 21 CFR §801.

STRICT LIABILITY

The FDA's position on who is and who is not considered a manufacturer has implications beyond cGMP regulations. The more significant issue focuses on the party who would be held strictly liable for product liability claims. Experts have suggested that it may be the hospital printing the device, the company that makes the printer or the software provider.[23] Yet this may not be the whole story.

Hospitals and research centers are not typically held strictly liable because medical products are considered incidental to the healthcare services rendered.[24] In most of the commonly cited cases, the bodily injuries in question did not involve devices owned and manufactured by the hospitals and research centers. If the hospital had been the holder of the 510(k) or PMA, which is a situation not anticipated or necessarily needed clinically for 3D-printed devices, then the courts' perspective regarding product liability *may* have differed.

Some have suggested other potential parties subject to strict liability may include the company manufacturing the actual printer or the software designer controlling the machine. However, it is questionable that such firms would be held strictly liable under a product liability claim any more than would makers of conventional subtractive manufacturing equipment and its controlling software. (For additional reading on the challenges surrounding 3D-printed devices and product liability law, see "Now That 3D Printing is Creating Medical Devices, What Regulatory and Liability Challenges Loom?")

Nevertheless, as discussed above, under most circumstances it is likely that the OEM will remain the primary responsible party under the strict liability doctrine now and in the foreseeable future. Notwithstanding that analysis, a hospital printing a device would not be exempt from liability and damages caused by its own negligence. However, product liability exposure is driven by the plaintiff-friendly strict liability standard. This supposition is based upon three principles discussed to this point:

1. Devices may not need to be "manufactured" at the hospital.
2. Even when it makes technical/commercial sense for onsite 3D manufacturing, it may be under circumstances that exempt hospitals as manufacturers (e.g., a PMA-approved system that treats a hospital as merely preparing the device).
3. Hospitals are not likely to be held strictly liable for products used in the course of delivering healthcare services.

Thus, the question of what party would sustain the majority of product liability risk is an interesting one. Yet, it may not become an essential factor in calculating the risks and benefits to hospitals utilizing 3D printing technology.

Under most circumstances it is likely that the OEM will remain the primary responsible party under the strict liability doctrine now and in the foreseeable future.

23 See the Brexis article and the Reed Smith article, both cited previously.
24 See Beck, J. "Hospital Strict Liability: A 50-State Survey." Reed Smith LLC, November 2012.

FDA Additive Manufacturing of Medical Devices Public Workshops

The additive manufacturing workshops held in October 2014 included 3D printing authorities in several industries and utilized resources of governmental agencies, academia and the private sector.[1] The two-day event focused on advancing the dialogue between industry and the FDA regarding the submission process and also addressing FDA concerns about the manufacturing technique.[2] The discussion was organized into three main topics:

Pre-printing considerations: *These include such topics as the intended use of the device, materials that can be used and certified, the printing process itself, raw material supply and software workflow. (The last-referenced topic may have either a minimal or significant impact on manufacturing depending upon whether the device is built to personalized specifications or is an off-the-shelf product.)*

Printing considerations: *These include printer control software, initial material properties that influence the printing platform, printing parameters (e.g., beam parameters, heating temperature, scanning speed, blending materials/possible chemistry changes), and quality control (e.g., process flow documentation, reproducibility, validation, revalidation, minimization of human elements, and ability to identify a poor-quality job during printing as opposed to relying on post-production testing).*

Post-printing considerations: *These include mechanical and physical properties, biocompatibility tests, initial cleaning of the device and sterilization processes.*

The substantial equivalence analysis combines all of these considerations (with the possible exception of software validation), while also evaluating performance data and requisite manufacturing standards (e.g., American Society for Testing and Materials).

The literature and workshop content reveal certain common questions about medical devices manufactured with this "new" technology. In **"FDA's View on 3-D Printing Medical Devices"**, *cited previously, the FDA's Stephen Pollack summarizes these questions as follows:*

- *How do you clean the device?*
- *How do you remove processing agents from the final product?*
- *How do you ensure biocompatibility?*

Pollack goes on to state that "they're not showstoppers, just questions." The same outlook also was affirmed in the Workshops.

These questions relate directly to evaluation of performance data. For example, the porosity characteristic alone could implicate several areas of performance data. These data elements include mechanical integrity tests, cleaning of excess residues from pores post-manufacture (i.e., "cleanliness," which can be detected in the biocompatibility tests) and sterilization performance.[3]

Biocompatibility tests are performed on non-sterile or sterile medical devices that contact the human body directly or indirectly. The extent of such tests varies, but they often focus on cytotoxicity, sensitization, irritation, systemic toxicity, biodegradation and pyrogen testing, among other issues.[4]

As this article was in production, the FDA released a draft guidance addressing design/manufacturing and testing considerations.[5] Before the FDA published these guidelines, they were on the agency's "B-list" of priorities, which suggests perhaps that the 3D printing process may not raise a high level of concern.[6]

1 Food And Drug Administration (FDA) Center For Devices And Radiological Health (CDRH) Additive Manufacturing Of Medical Devices Public Workshop, October 9, 2014. ("10/9/14 Workshop").
2 See this site for the workshop agenda, while the following two sites – here and here – provide presentation transcripts.
3 A biocompatibility evaluation must be conducted in accordance to International Standard ISO-10993.
4 See "Use of International Standard ISO-10993, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing"," June 16, 2016. See also page 35 of the FDA Guidance document.
5 "Technical Considerations for Additive Manufactured Devices," May 10, 2016.
6 The CDRH Fiscal Year 2015 (FY 2015) Proposed Guidance Development and Focused Retrospective Review of Final Guidance lists "3D Printing (Technical)" as one of seven possible topics that the Agency intends to publish "as resources permit." Also see Scott, B. "3-D Printing Guidance Only a B-List Priority for FDA," Epstein, Becker & Green, P.C.'s *Health Law Advisor*, March 10, 2015.

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