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FDA finalizes 3D printing guidance

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Introduction

On December 5, 2017, the U.S. Food and Drug Administration (FDA or the Agency) finalized its "leapfrog guidance" entitled, "Technical Considerations for Additive Manufactured Devices" (the final guidance). Although the final guidance technically applies only to medical devices, its finalization advances the Agency's policy framework for 3D printing of all medical products, including medical devices, medications, and tissue products. The final guidance closely resembles the May 10, 2016, draft guidance described in our prior alert, with few modifications. The most notable additions are outlined in this alert.

The guidance continues to be based off of information gathered in the October 8–9, 2014 workshop. Nevertheless, FDA continues to focus its efforts in this area, hosting a related workshop on 3D printed models used in a clinical setting on August 31, 2017. The purpose of this meeting was to identify current best practices, levels of benefit and risk for different intended uses, and gaps in clinical evidence needed to perform effective regulatory review. A white paper summarizing the results of the workshop is expected, but has yet to be released.

Like the draft guidance, the final guidance provides recommendations only for manufacturing considerations related to additive manufacturing (AM) devices, noting that AM devices generally are expected to follow the same regulatory pathway as non-AM devices of the same type. And, although the final guidance focuses on medical devices, the Agency has also laid the groundwork for the regulation of 3D-printed drug products, as further discussed below.

Design and Manufacturing Process Considerations

FDA has always required that manufacturers establish robust quality systems that govern all aspects of the manufacture of finished medical devices, irrespective of the type of manufacturing processes employed. When looking at the various processes and techniques employed for AM, including powder fusion, stereolithography, fused filament fabrication, direct metal laser sintering, and liquid-based extrusion, it becomes clear that AM introduces nuances to the manufacturing process that can impact the finished device. These nuances, which require specific consideration, can extend to all phases of the manufacturing process, from development, production, and process validation to final, finished device testing. The final guidance provides a useful framework for evaluating these issues.

As a starting point, FDA continues to suggest creating a production flow diagram that identifies all critical steps involved in manufacturing the device, from the initial design to post-processing of the final device. Further recommendations address device design, software workflow, material controls, post processing, process validation and acceptance activities, as well as quality data. Although the recommendations in the final guidance closely mirror the draft guidance, the final guidance includes the additional recommendations in the following key areas:

— *Patient-Matched Devices*. The final guidance continues to devote significant attention to addressing additional considerations for patient-matched devices (PMDs), which are uniquely suited to AM manufacturing techniques. The final guidance reiterates and expands upon the considerations related to the effects of imaging and interacting with design models that were articulated in the draft guidance. Additionally, the final guidance outlines new considerations for working with complex design files, which may create difficulties with file conversions. This issue is particularly acute for PMDs, for which file conversions are often performed every time a device is built. The final guidance also recommends proper management of personally identifiable information (PII) and protected health information (PHI) in accordance with U.S. Health and Human Services (HHS) Guidance through appropriate cybersecurity measures.

— *Software Workflow*. The manufacture of AM devices often requires use of multiple software programs at various stages of the process; thus, files must be compatible across software applications. The final guidance expands upon the recommendations for file format conversions in the draft guidance, noting that file critical attributes and performance criteria should be verified as part of the software workflow validation to ensure expected performance, particularly for PMDs.

— *Process Validation and Acceptance Activities*. The final guidance has an increased focus on risk-based determinations for appropriate validation activities generally and on process validation activities specifically, recommendations for which have been articulated throughout the guidance. For example, the final guidance articulates new recommendations for process validation, which should be based on the risk profile of the device. However, the guidance specifically recommends that Operation Qualification (OQ) of the printing process includes challenging the build volume placement to establish control limits that result in product that meets all predetermined requirements.

— *Device Modifications*. Whether a modification of an existing device requires a new clearance by FDA is typically tied only to the design of the device. For AM devices, design and manufacturing are more intertwined. However, the final guidance clarifies that existing guidance for post-market changes can be used to assess whether a change to an AM device requires process revalidation and/or submission to FDA. Some potential triggers for revalidation specific to AM include changes to the software or software workflow, material changes, changes to the spacing or orientation of devices or components in the build volume, physically moving a manufacturing machine to a new location, and changes to the post-processing steps or parameters.

Premarket Device Testing Considerations

The premarket device testing considerations articulated in the final guidance are nearly identical to those in the draft guidance; however, additional attention has been placed on the impact of increased design complexity on the removal of manufacturing residual materials (media blast, cleaning, etc.) and sterilization. The final guidance notes that the cleaning and sterilization process validations should account for the complex geometry of AM devices under worst-case conditions. The final guidance specifies that highly porous regions are expected to be difficult to clean in comparison to devices made with other manufacturing methods, and can also greatly

increase the surface area of the device. Therefore, submissions should include an overview or summary of manufacturing residue removal processes and information (e.g., testing procedure and data). The extent to which manufacturing material residue must be reduced is determined on a case-by-case basis considering characteristics such as: manufacturing processes, intended use, materials, type and duration of exposure, intended anatomical location, and type of device. As discussed in more detail below, it is important to note that recently these questions are being asked more frequently and with greater specificity by the Agency during the 510(k) review process.

Next on the Horizon: 3D Printed Drugs

Although FDA's recent guidance focuses on medical devices, the Agency laid the groundwork for the regulation of 3D-printed drug products. Patients have been benefiting from 3D printed drug products since 2015, when FDA for the first time approved the use of the bioprinting technology, ZipDose Technology, for Aprecia Pharmaceutical Co.'s Spritam (levetiracetam) tablets prescribed for epilepsy. The technology created a porous formulation to help with bioavailability and patient uptake by disintegrating in the mouth with a small amount of water, thus opening the possibility for patients with difficulties swallowing. As Dr. Gottlieb stated in the December 4 press release, "This is likely just the tip of the iceberg given the exponential growth of innovative research in this field," namely in the areas of skin cell and organ development. Several drug manufacturers have engaged FDA regarding the use of 3D printing through the Center for Drug Evaluation and Research's (CDER) Emerging Technology Program, a program designed to allow industry representatives access to FDA to discuss, identify, and resolve potential concerns regarding the development and implementation of a novel pharmaceutical manufacturing technology prior to filing a regulatory submission. FDA is advancing this technology by conducting research to determine the impact, if any, of 3D printing on inactive ingredients and other drug components, and on quality control processes. And in its latest effort, CDER's Office of Testing and Research is conducting research to understand the effects of material attributes, such as the critical parameters affecting the quality, safety and efficacy of a drug product and to develop testing methods that can predict the performance in different patients. The technology has the potential to develop unique dosage forms with characteristics that cannot be obtained using conventional manufacturing processes, which could be especially helpful for the treatment of children, the elderly, and other special populations. The agency intends to review the regulatory considerations for bioprinting biological, cellular and tissue-based products to evaluate whether additional guidance is needed beyond the regenerative medicine policy framework announced last month (and previously written on here). We will be closely watching as FDA continues to shape the regulatory framework for this innovative technology, and will provide timely updates.

Discussion

Based on experience with FDA's review of regulated 3D printed medical devices, and as outlined in the final guidance, FDA's overall criteria for evaluation and testing of 3D printed devices are largely similar to those associated with traditionally manufactured devices. However, while 510(k) and de novo premarket submissions do not typically include any manufacturing information, the final guidance makes it clear that FDA will expect to review certain 'manufacturing' information, such as the orientation of a printed object and the printing location. Over the years we have seen variability in FDA's handling of this issue in its review of 510(k) notices for AM devices. In the past, most 510(k) reviews focused exclusively on the finished device, without delving into AM aspects of the manufacturing process. More recently, 510(k) reviews for digital and physical anatomical outputs have delved deeper into the AM manufacturing processes and specifically discussed the additive manufacturing equipment and processes, including testing to confirm removal of media blast and cleaning residuals. Other

510(k) clearances have limited use of the 3D printed device to visualization and education purposes, with only the software functionality outlined in the indications for use. Based on very recent experiences, FDA is continuing to evolve their views on what is considered in the scope of the 510(k) review, with some additional testing requests occurring late in the review process after consulting with Agency technical experts. While many factors may have contributed to prior variability, our more recent experience, coupled with the final guidance, signals an effort by FDA to better define this scope.

Notwithstanding the above discussion, the issues related to AM devices remain complicated for companies to manage in the context of a 510(k) submission, particularly from a software perspective. In many instances, multiple software programs (including custom, off-the-shelf, or third-party-cleared software programs) are used in the overall process flow involved in the creation of 3D printed devices. The final guidance updates the discussion of two types of software involved in the additive manufacturing process—Design Manipulation Software and Build Preparation Software—used in the design and manufacturing of the AM device. Although certain software validation and revalidation activities are clearly required from a quality system perspective, FDA does not appear to view such software as part of the device design to be included in a premarket submission, as the final guidance explicitly states that it addresses only manufacturing considerations. Furthermore, the guidance recommends that companies engage with FDA through the pre-submission process to obtain detailed feedback about the technical information needed to support pre-market submission, if such information is not clear.

Conclusion

Overall, the final guidance does not depart significantly from the draft guidance; however, the final guidance makes clear that use of AM technology to manufacture a device is not expected to greatly change the regulatory pathway or the testing requirements of the final, finished product. Like the draft guidance, the final guidance focuses primarily on the regulatory requirements for primary device manufacturer and does not discuss if and how historically unregulated entities, such as 3D printer manufacturers, 3D printing service providers, hospitals that are performing in-house 3D printing, or contract dental laboratories, are impacted.

From a practical perspective, FDA has been seeking very specific manufacturing information and related testing information on a case-by-case basis not previously provided for traditionally manufactured devices. In addition, while the final guidance explicitly addresses AM devices, the principles are likely also relevant to other FDA regulatory products made using the same methodologies, such as drug or tissue-based therapies.

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