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FDA Takes on 3D Printing In New Draft Guidance

With 3D printing — also known as additive manufacturing — taking off, the FDA is playing catch up to provide needed industry guidance.

To that end, the FDA has offered its preliminary thinking on technical considerations specific to 3D-printed devices.

In draft guidance released May 10, the FDA concentrates on two topic areas: design and manufacturing considerations and device testing issues.

The first section addresses what sponsors should keep in mind to meet quality system requirements, while the latter delves into what information should be provided in 510(k)s, PMAs, HDEs, IDE applications and de novo requests for 3D-printed devices.

As the document notes, there are a number of technologies and processing steps that can be used in creating a 3D-printed medical device; therefore, it's essential to identify each throughout in the

(See **3D Guidance***, Page 2)*

Expert: China's New Device Standards Will Reduce Regulatory Uncertainty

China's new technical standards for medical devices provide much needed clarity to regulations that previously were open to different interpretations, experts said.

The 186 new standards are a tangible set of guidelines that "create consistent review standards the industry has been clamoring for," said Helen Chen, managing director and partner at L.E.K. Consulting in Shanghai.

"CFDA is addressing the concerns raised by industry, including AdvaMed, that the lack of standards and often inconsistent interpretation by individual CFDA reviewers add complexity and opacity to an already onerous registration process," Chen said.

(See **China***, Page 4)*

3D Guidance, *from Page 1*

design and manufacturing phases. The agency recommends creating a production flow diagram to document the steps from the initial design phase to post-processing.

Further, the cumulative effects of previous processes on the final device or component should be outlined to help determine the root cause of any potential failure.

The document also notes that manufacturers should consider whether the device will be of a predetermined size, as well as how the product can be tailored to a patient's unique anatomy.

Software

How software from different manufacturers will interact also should be addressed to avoid errors during file conversion. For example, images from MRIs or CT scans, design manipulation software for patient-matching and machine-readable files all have unique standards, coordinate systems and default parameters.

"Errors in file conversion can negatively impact final finished device and component properties, such as dimensions and geometry," the document notes.

Stakeholders are advised to test all file conversion steps using worst-case scenarios. "Factors that may cause unexpected conversion failures, such as changes to the software used, may trigger the need for revalidation," according to the FDA.

The FDA recommends that final device files "should be maintained and archived in robust, standardized formats that are able to store AM-specific information."

In addition, the document includes information on the type of information for testing, addressing biocompatability and labeling considerations. For the latter, the document says each patient-matched device should include a patient identifier; details identifying use, such as anatomical location; and the final design iteration or version used to produce the device.

While providing a broad overview of manufacturing and testing, the document doesn't cover the use of biological, cellular or tissue-based products in AM. "Biological, cellular or tissue-based products manufactured using AM technology may necessitate additional regulatory and manufacturing process considerations and/or different regulatory pathways," according to the document, which says that any questions about products containing these materials should be directed to representatives from CBER.

The document — which builds on discussions from an October 2014 workshop on AM — is what the agency calls a "leap-frog guidance," which aims to provide the agency's initial perspective on emerging technologies.

The FDA isn't the only entity touting 3D printing for devices recently. UPS and the Consumer Technology Association released a study on the rise of 3D printing that highlighted the processes' success in the medical device industry. According to the paper, the medical device arena is the third largest 3D printing market, and 98 percent of hearing aids worldwide are manufactured using the process.

Read the draft guidance here: www.fdanews.com/05-16-16-FDAAdditive.pdf. Check out the study here: www.fdanews.com/05-16-16-ups-CTA.pdf.

FDA Extends Comment Period On GMPs for Hearing Aids

The FDA is extending the comment period to June 30 on draft guidance covering good manufacturing practices for hearing aids.

The agency released draft guidance in January, Streamlining Regulations for Good Manufacturing Practices for Hearing Aids, which clarifies the difference in regulatory requirements between hearing aids and personal sound amplification products (*IDDM,* Jan. 8).

The agency also held a public workshop in April to outline its perspective on GMPs and to seek stakeholder input on alternative models for regulating hearing aids.

Read the draft guidance here: www.fdanews.com/05-10-16-HearingAidsNotice.pdf. — Joya Patel

FDA Issues Guidance on Infectious Disease NGS Dx Devices

The FDA has provided details on how it plans to regulate diagnostics that detect infectious disease organisms, antimicrobial resistance and virulence markers.

The agency spells out the data it expects to see in a submission for infectious disease next-generation sequencing (NGS) diagnostic devices, in draft guidance released May 13.

Tagged as Class II devices, the FDA will regulate infectious disease NGS Dx devices based on a "one system" approach, similar to the way it regulates molecular-based diagnostic devices. The guidance notes that in contrast to human sequencing diagnostics, infectious disease sequencing diagnostics generally require rapid and actionable results, "as delayed or incorrect diagnoses can result in fatalities."

The broad range of specimen types and the diversity of infectious disease agents in a sample don't allow for straight-forward pre-analytical testing, the FDA said.

The guidance was drawn from stakeholder input during an April 13, 2015 meeting that stressed the need for more advanced testing to better detect and identify infectious disease organisms. Stakeholders stressed that next-generation sequencing can replace previous methods with a single approach.

"Documentation of the locked-down bioinformatics pipeline, including all required steps, from handling the 'raw' sequencing data to producing the diagnostic output, should be provided and should demonstrate robustness for clinical microbiology use," the guidance says.

The sequencing system is made up of the following steps:

- Specimen collection;
- Specimen preparation for sequencing;
- Sequencing/chemistry/data collection;
- Data storage/data analysis;
- Report; and
- Possible oversight dependent on use of data in final diagnostic report.

The guidance proposes the use of an alternative comparator to validate NGS-based tests for infectious diseases. To that end, the agency developed the FDA-ARGOS [FDA dAtabase for Regulatory Grade microbial Sequences] database to supply validated regulatory-grade microbial genomic sequence entries collected from public databases.

To qualify as a regulatory-grade genomic sequence entry, the microbial organism or resistance and virulence marker has to be explicitly identified prior to sequencing.

The guidance outlines requirements for:

Benefit-risk analysis: Premarket submission should include a discussion of potential benefits and risks associated with the device, as well as risks of device failure.

Device description: Manufacturers need to demonstrate precise intended use for targeted and agnostic sequencing approaches and conditions, including test methodology, ancillary reagents, controls and interpreting test results and reports.

Device validation: The FDA recommends seeking advice before undertaking any clinical or analytical validation studies to discuss whether additional recommendations are available due to new advancements in this fast moving field. Manufacturers should include documentation in the form of diagrams and pictures displaying the flow of information on analytical performance, instrumentation and software and clinical evaluation.

Device modification: Submissions should also include a detailed procedure for acceptance criteria, risk analysis, database updates and validation testing.

The guidance does not apply to products intended to screen for communicable disease, which are classified as high-risk Class III devices.

Stakeholders may comment on the draft through Aug. 11. Read the draft guidance here: www.fdanews.com/05-12-16-DraftGuidanceIDNGSDxDevices.pdf. Check out the FDA-ARGOS database here: www.fdanews.com/05-12-16-FDAARGOSDatabase.pdf. — Joya Patel

China, *from Page 1*

The 186 new standards, 42 of which are mandatory, include standards devices need to meet, parameters for testing, rules of inspections and other technical requirements, she said (*IDDM*, May 9).

Device manufacturers will be mostly affected when they submit new applications and when they renew existing licenses. Chen recommends that companies retool their processes before they submit applications.

"In general, we expect that the bigger impact would come during license renewal time, where the products which no longer qualify under the new standards are withdrawn from the market," Chen said.

Katherine Wang, partner at Ropes & Gray LLP, said the changes will also affect manufacturers' research and development of new devices. She noted that devicemakers currently comply with mandatory industry requirements, but there have been no concrete national technical standards.

Manufacturers who fail to meet the mandatory standards face significant risk, Wang said, including "significant legal risks, confiscation of products, fines, revocation of licenses and permits."

For manufacturers already in compliance with the mandatory standards, the technical review process will be streamlined, Chen said. If standards are not specified, manufacturers need to demonstrate specifications that would ensure safety and efficacy for CFDA approval.

As a result of the tightened standards, products registered under a lax regime with lower quality and efficacy will naturally be weeded out of the system.

Before multinational devicemakers can market their products in China, they need to designate a local registered agent and assign the product into one of three risk classes.

The mandatory industry standards will come into effect on Jan. 1, 2018 and the recommended standards become effective on Jan. 1, 2017.

Read the CDFA announcement here (in Chinese language): www.fdanews.com/05-11-16-CFDA74thAnnouncement.pdf. A link to standards of each device is here (in Chinese language): www.nifdc.org.cn/CL0823/. — Joya Patel

Canada Brings Reprocessors Up to Speed on Regulations

Manufacturers of reprocessed single-use devices will have an extra year to comply with Canadian medical device regulations.

Health Canada compliance deadlines for reprocessed devices had originally been set for September 2016, but after meeting with stakeholders, the agency extended the deadline to September 2017 to provide manufacturers and reprocessors adequate time to meet the new requirements.

Companies engaged in reprocessing and distributing single-use devices will be held to the same requirements for licensing and registration as manufacturers of new devices according to Canadian Medical Devices Regulations. This includes requirements for:

- Obtaining licensing;
- Compliance with quality system management;
- Device labeling;
- Investigating and managing complaints;
- Maintaining distribution records;
- Conducting recalls and reporting incidents; and
- Keeping Health Canada updated on any changes made to information in the license application.

Labels should clearly identify reprocessors as their manufacturers alongside instructions for safe reuse. Any single-use symbols should also be removed from reprocessed device labels.

The updated requirements do not apply to devices reprocessed on-site at hospitals; these products will continue to be overseen by provincial authorities.

Read the Health Canada Notice here: www.fdanews.com/05-10-16-HealthCanadaNotice.pdf. — Joya Patel

FDA Provides Guidance On 522 Postmarket Surveillance

In a move aimed at ensuring the safety and effectiveness of marketed products, the FDA has updated its thinking on 522 postmarket surveillance studies for Class II and III devices.

The guidance — issued May 16 — provides an overview of Section 522 of the FD&C and is intended to help medical device manufacturers fulfill related obligations. It also offers tips on the format, content and review of postmarket surveillance plans.

Section 522 gives the FDA the authority to require postmarket surveillance of devices that meet the following criteria:

- Their failure likely would cause serious adverse health consequences;
- They would see significant use in pediatric populations;
- They are intended to be implanted in the body for more than one year; or
- They are intended to be a life-sustaining or life-supporting device used outside a device user facility.

New Sections Added

Changes from the draft version — which was issued Aug. 11, 2011 — include a new section on the timing for issuing a 522 order and the start of postmarket surveillance.

The section informs manufacturers that the agency may issue a postmarket surveillance order at the time of device approval or clearance "or any time thereafter." The manufacturer thus is required to begin postmarket surveillance no later than 15 months after the day the order is issued. That gives manufacturers three more months than what was provided for in the draft version.

Another change is the rewording of situations that could trigger a postmarket review.

The new document says the agency could order surveillance "to obtain more information on device performance associated with real-world clinical practice." That marks a dramatic change from the draft version, which said the agency could order postmarket surveillance "to obtain more experience with a change from hospital use to use in the home or other environment."

The guidance also adds color to the discussion of the process used to determine whether a problem potentially linked to a medical device warrants postmarket surveillance. The issue is reviewed by a pre-522 team, consisting of epidemiologists, clinicians or other experts, with an eye toward providing a recommendation on whether a 522 order should be issued.

The final document expands one of the elements the inspection team might review, providing examples of the potential data sources that could trigger a public health question that needs to be addressed. Examples include scientific concerns resulting from a review of a premarket submission, a recall and medical device reports.

In addition, the document greatly expands the section on changing an approved postmarket surveillance plan.

While the draft version included only two sentences on this topic the final document offers four paragraphs. For example, it explains that the FDA only will accept submissions that are "substantially complete," adding that a not acceptable letter could be issued to those that fail to meet this standard.

"Unless FDA approves the revised surveillance plan, the manufacturer remains responsible for completing the approved surveillance plan. Failure to meet the milestones and timelines outlined in the approved surveillance plan may result in enforcement action by FDA," the document warns.

Finally, the document also includes an appendix that lays out a Section 522 administrative checklist review.

Read the document here: www.fdanews.com/05-16-16-postmarket.pdf.

Appeals Court Smacks Down Endotach in Patent Spats

A federal appeals court gave Cook Medical and Medtronic wins in separate patent disputes with Endotach this month.

In a terse May 6 decision, a three-member panel of the U.S. Court of Appeals for the Federal Circuit upheld a finding in a dispute involving the ’154 and ’417 patents, which were licensed to Acacia Research by the inventor’s widow. Acacia is the parent of Endotach and bills itself as “an intermediary in the patent market.”

Frisco, Texas-based Endotach had sought damages for alleged patent infringement related to Cook’s sales of the following grafts for vascular procedures: Zenith AAA, Zenith Flex, Zenith Renu, Zenith Fenestrated and Zenith TX2. A judge in the U.S. District Court for the Southern District of Indiana was not persuaded by Endotach’s arguments, ruling in Cook’s favor in January 2015.

Cook wasn’t the only company hauled into court for allegedly infringing these patents, with Endotach also suing Medtronic over sales of the Endurant and Endurant II AAA stent grafts. The suit was transferred from Florida to the U.S. District Court for the Northern District of California, where Medtronic requested a stay to allow for the completion of a review by the U.S. Patent Trial and Appeal Board of all claims asserted by Endotach related to the ’417 patent. Endotach had dropped the other patent from the dispute.

The request, which Endotach did not fight, was granted. In March 2015, the PTAB ruled that each of the asserted claims of the ’417 patent are unpatentable, a decision the company appealed to the Federal Circuit. However, the three-judge panel seemingly was not impressed with Endotach’s arguments, offering no explanation in a May 6 ruling in Medtronic’s favor.

In June 2012, Endotach sued W.L. Gore in Florida for infringing the patents. It voluntarily dismissed the case with prejudice in October of that year.

Australia Urges Caution With Reprocessed Duodenoscopes

Two major manufacturers of duodenoscopes marketed in Australia have initiated recalls to address contamination after reprocessing.

Olympus has recalled products in Australia to update its Instructions for Use regarding reprocessing and to modify its device. Similarly, Pentax recalled its video duodenoscope to update its Instructions for Use regarding reprocessing.

As a result of increased cross-contamination between patients due to reprocessed duodenoscopes, the TGA is urging health professionals to be alert of potential changes to some devices’ Instructions for Use labeling.

The TGA received one report this year of a duodenoscope that tested positive to intestinal bacteria despite repeated reprocessing efforts. The agency urges health facilities to report cases of contamination following cleaning and sterilization.

In January, the FDA released a report on safety regulations making a number of recommendations for preventing contamination (*IDDM*, Dec. 31, 2015).

In related news, the TGA is working with manufacturers of heater-cooler devices used in cardiothoracic surgery to ensure that infection risks are mitigated.

Cardiac procedures that use implanted medical devices alongside heater-cooler devices have been reported to cause non-tuberculous mycobacterium infections. These devices include oxygenator heat exchangers, cardioplegia heat exchangers and warming/cooling blankets.

The TGA is advising manufacturers on providing updated cleaning and disinfecting instructions. Manufacturers must keep updated versions of Instruction for Use, provide additional information on recalls and product corrections.

The FDA has a total of 40 medical device reports of infection associated with heater-cooler devices as of April. — Joya Patel

Califf: Off-Label Guidance One of FDA's Top Priorities

Addressing off-label promotion is one of the agency's front burner priorities for 2016, FDA Commissioner Robert Califf said.

Current off-label policies were developed during a time when physicians had limited sources for gathering and processing information, Califf said, noting that current policies are dated, and the FDA needs to reevaluate its regulations on drug advertising and promotion in light of current jurisprudence around the 1st Amendment.

The agency plans on working collaboratively with industry to create comprehensive guidelines for off-label products, he told the Medical Device Manufacturing Association meeting.

Panelists lauded the government's evolving perspective on off-label products, citing the cases of Amarin and Pacira as first amendment victories.

Under the Amarin ruling, the agency is bound by the terms of an August 2015 injunction permitting Amarin to promote cholesterol drug Vascepa off-label using court-approved language to ensure that the information is truthful and not misleading (*IDDM*, March 11).

Industry experts have said the Amarin case would have broad implications for devicemakers.

Benjamin Wallfisch, associate at Norton, Rose, Fulbright, cautioned devicemakers not to jump the gun when it comes to promoting a product before it is ready. He recommends that companies work with their marketing teams to make sure their product communications don't straddle a blurry line while the agency clarifies its regulations. — Joya Patel

Expertise Outweighs Conflict of Interest in FDA Adcom Meeting

The FDA granted a waiver to allow a device expert with a potential conflict of interest to participate in an advisory committee meeting.

Richard Page, chairman of FDA's Circulatory System Devices Panel, acknowledged a financial conflict of interest because he is employed by the University of Wisconsin School of Medicine and Public Health, which was a clinical site for St. Jude Medical's Amplatzer PFO Occluder study.

On May 24 the panel will discuss, make recommendations and vote on the PMA.

The FDA noted Page was not directly involved in conducting the RESPECT trials, or providing input on investigator activities. As chair of the Department of Medicine, he also was not personally involved in industry grants, contracts or other relationships.

The waiver cites his expertise in clinical trial design, benefit-risk analysis, in-depth understanding of treatment strategies and knowledge of cardiovascular diseases.

Read the waiver notice here: www.fdanews.com/05-10-16 WaiverCirculatorySystemDevicesPanel.pdf. — Joya Patel

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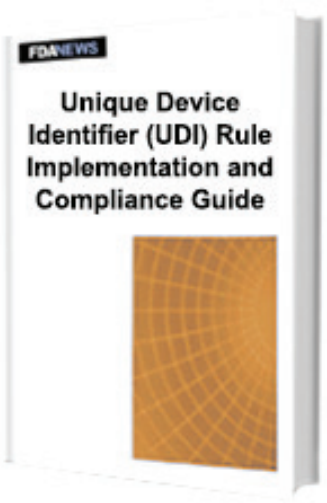

Unique Device Identifier (UDI) Rule Implementation and Compliance Guide

The rush to compliance is in full swing. By Sept. 24, 2015, all implantable, life-saving or life-supporting devices must comply with the new UDI requirements. By 2018 all devicemakers must be in compliance.

You'll need to understand what UDI is … who it applies to … what the exceptions to the rule are … what deadlines you must meet … what UDI issuing agencies are ... and how to work with them. Thankfully, help is here.

With **Unique Device Identifier (UDI) Rule Implementation and Compliance Guide**, you'll gain a clear understanding of this complex new rule and learn to work with it more successfully. You will learn:

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Understanding China's New Medical Device Regulations

China completely revised its medical device regulations in 2014, and the changes are beginning to take effect NOW.

These revised regulations touch on many areas: research and development, approval, manufacturing, and distribution of medical devices.

And they affect all devices — those already on the market as well as the ones still in development.

If you want to continue — or begin — to sell your medical devices in China, understanding the new rules is absolutely essential.

To gain mastery of these important regulatory changes, there's no better resource than the new FDAnews management report, **Understanding China's New Medical Device Regulations**.

This report is NOT broad brush coverage. You'll learn real specifics as you work your way through the incredible detail of this report, covering such areas as:

- Changes in the basic requirements for registering a medical device in China. (Some devices — but not all — that once needed to be registered no longer do.)
- CFDA has greater enforcement power to order recalls, terminate sales, freeze imports and, most importantly, issue larger penalties to and even shut down devicemakers.
- CFDA can impose moratoriums on devicemakers that fail to satisfy registration requirements and, in serious cases, even revoke their licenses.
- Revisions to medical device classification rules — including new requirements for registering class I devices.
- And much more

With implementation of the new Chinese rules already under way – and more changes coming — it's very clear that to sell medical devices in China in 2015, you must quickly get up to speed on the new and revised requirements.

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