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IN THIS ISSUE

Health Canada Issues Final Guidance On 3D-Printed Implantable Devices

Health Canada issued final guidance for devicemakers on supporting evidence required for submitting applications for 3D-printed implantable devices.

In response to comments on the agency's November 2018 draft, the final guidance makes the distinction between patient-specific devices with patient-matched devices, to align with the International Medical Device Regulators Forum (IMDRF)'s definitions for personalized medical devices.

The updated guidance covers the evidence required to support pre-market Class III and Class IV license applications for implantable devices manufactured by 3D printing—including design and manufacturing processes, material controls, device testing and labeling of 3D-printed devices.

The agency clarified that where the device is patient matched, rather than manufactured to predetermined sizes, the description

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

Senator Demands Answers From Companies Over Duodenoscopes

Washington Democratic Sen. Patty Murray is demanding answers from the leaders of three device companies at the center of an ongoing FDA investigation of contaminated duodenoscopes that regulators worry are spreading deadly bugs.

"I remain concerned about the risk of infection posed by these devices and [I am] committed to ensuring rigorous oversight," Murray said in three separate letters to Olympus, Pentax and Fujifilm.

Murray is the ranking member on the Senate Health, Education, Labor and Pension Committee, which oversees the drug and device industry and its regulators.

Last month, the FDA threatened to take regulatory action against the three devicemakers after analyses found that the contamination rates of

(See **Duodenoscopes**, *Page 2)*

Guidance, *from Page 1*

should include an overview of the printing process from acquiring the patient image to device design, printing and post-printing processing steps. Sponsors should include flow charts, key design parameters and whether parameters may be altered to be patient matched, as well as any critical features including the boundaries of dimensions.

For the device description, manufacturers should include the starting material, a description of the 3D printing method and an overview of the manufacturing process, the agency said. The description should clarify whether the entire device or only a component of the device is 3D printed.

Further characterization of the starting material may be required in specific cases, the agency said.

In comments on the draft guidance, AdvaMed had asked Health Canada to clarify the different expectations for Class III and IV devices. "The license applications guidance asks for significantly less information on manufacturing and quality controls for Class III devices," AdvaMed said. "It is unclear in the 3D printing guidance if this expectation carries through to 3D-printed devices, or if there are higher expectations for Class III 3D-printed devices."

AdvaMed pressed the agency to clarify what it expects in an application versus what would be more appropriate for review during quality management system audits (*IDDM*, Nov. 16, 2018).

In response, the final guidance includes an appendix that provides additional information on the supporting evidence required for Class III and Class IV medical devices as well as a table of contents folder for submitting license applications.

The final guidance notes that the same data requirements apply to 3D-printed devices as those for conventional devices in terms of their characterization and evidence of safety and effectiveness, including physical and mechanical bench testing, biocompatibility testing, software validation and clinical evidence.

Preclinical performance testing should be conducted on the final, finished device subjected to all post-processing, cleaning and sterilization steps. A detailed summary is required for each test, the agency said.

The guidance also lists additional considerations for device performance and shelf life, software verification and validation, biocompatibility tests and clinical studies (*IDDM*, Nov. 16, 2018).

Read the final guidance here: www.fdanews.com/05-09-19-HealthCanada.pdf.

Duodenoscopes, *from Page 1*

the scopes had actually risen since regulators first flagged the devices in March 2018 (*IDDM*, April 12).

Murray says she finds the results "troubling" and, while she acknowledges the companies seem to have taken some steps, it's still "unacceptable that one in 20 patients who undergo a procedure using a duodenoscope may acquire an infection as a result of that procedure—even when hospitals have followed cleaning instructions correctly."

In her letter, Murray demands that the companies provide copies of each scope's Medical Device Report since January 2017 and also the rates of contamination in FDA-ordered sampling studies.

She also asks them to explain when they'll finish the post-market analysis that the FDA has ordered, whether the companies have done any analyses of the FDA's interim findings and how the companies plan to address findings in their postmarket studies.

Finally, Murray asks whether they think the devices are actually safe, what feedback they're getting from users and whether the companies have "engaged in any effort to re-design or modify" their devices.

A Fujifilm spokeswoman said the company will "work with all stakeholders, including regulators and lawmakers to ensure the safe use of" its devices. Efforts to reach Olympus and Pentax for comment were unsuccessful.

Read Murray's letter here: www.fdanews.com/05-09-19-Murrayletter.pdf. — Bill Myers

CMS Proposes to Boost Payments For Breakthrough Devices

The Centers for Medicare and Medicaid Services proposed a new rule that would increase payments for breakthrough medical devices.

The CMS rule proposes an alternative new technology add-on payment pathway for a medical device that receives FDA marketing authorization and has received breakthrough device clearance.

Although the FDA's breakthrough designation can help expedite the development and review of transformative new devices that meet expedited program criteria, "CMS believes it is appropriate to similarly facilitate access to these transformative technologies for Medicare beneficiaries," the agency said.

Marketing authorization of a breakthrough device could lead to situations where the evidence base for demonstrating substantial clinical improvement has not fully developed at the time of FDA approval, CMS said, so it would also revise its substantial clinical improvement criterion under the inpatient prospective payment system (IPPS) new technology add-on payment policy.

CMS is proposing that if a device is cleared by an expedited program, it would consider the product new and not substantially similar to an existing technology for purposes of the new technology addon payment. Under the proposal, the device would only need to meet the cost criterion to receive the add-on payment. This change would begin with applications received for new technology addon payments for fiscal year 2021.

In the proposed rule, CMS discusses potential revisions to the substantial clinical improvement criterion currently used to evaluate applications for the new technology add-on payment under the IPPS and the transitional pass-through payment for additional costs of innovative devices under the outpatient prospective payment system.

Read the proposed rule here: www.fdanews.com/05-09-19-CMS.pdf.

FDA Issues Final Guidance On Bench Performance Testing

The FDA issued final guidance recommending what information devicemakers should include in test report summaries, test protocols and complete test reports for non-clinical bench performance testing for their premarket submissions.

Device premarket submissions include premarket approval applications, humanitarian device exception applications, 510(k) submissions, investigational device exemption applications and de novo requests.

The guidance, which replaces draft guidance issued in May 2018, defines non-clinical bench performance testing as performance testing, performed by either a device manufacturer or a third-party testing facility, which encompasses all bench testing and will be dependent on the specifics of the actual device or device type.

Non-clinical bench performance testing includes mechanical and biological engineering performance (such as fatigue, wear, tensile strength, compression, burst pressure); bench tests using ex vivo, in vitro, and in situ animal or human tissue; and animal carcass or human cadaveric testing.

The agency clarified that non-clinical bench performance testing excludes biocompatibility evaluation, reprocessing or sterilization validation, human factors, software verification and validation, and computational modeling.

Devicemakers should include test report summaries of the conducted testing in all premarket submissions and complete test reports when appropriate. The agency advised that complete test reports are not necessary for special 510(k)s or for tests that have been provided a declaration of conformity to an appropriate agency-recognized consensus standard (*IDDM*, June 1, 2018).

Premarket submissions should discuss how the non-clinical bench performance test results support the overall submission as well as conclusions from the testing.

(See **Testing**, *Page 4)*

FDA Wants Sponsors To Flag Real-World Evidence

The FDA may start accepting real-world evidence in support of device applications, but sponsors need to identify the sources of real-world evidence they're using in advance, the agency said.

Sponsors should say in their cover letters whether they hope to use real-world evidence to support safety or efficacy, to change a label, or to comply with a post-marketing requirement, the FDA said in a new draft guidance.

The guidance draws a line between real-world data—information about patients' health status or healthcare delivery "routinely collected from a variety of sources," including electronic health records, medical claims or billing data—and clinical evidence from analysis of real-world data.

"At the end of the day, care of an individual patient should be informed by reliable evidence derived from studies reflective of their personal *and* clinical story," said FDA Principal Deputy Commissioner Amy Abernethy in announcing the draft guidance.

Sponsors might use real-world evidence as external controls in single arm trials, to establish efficacy with observational studies, or in clinical trials or observational studies designed to meet post-marketing expectations.

Regulators only want to track real-world evidence that relate to specific products or regulatory decisions, so sponsors don't have to flag natural histories used to establish a clinical outcome test or biomarker, feasibility studies involving real-world evidence or studies that use real-world data "to perform exploratory analyses and generate hypotheses," the draft guidance states.

Since the passage of the 21st Century Cures Act, the FDA has increasingly embraced the potential of real-world evidence. Bids are due at the end of this month on the agency's massive Sentinel database which will include one of the world's largest real-world databases. The agency is also running experiments to see whether real-world evidence might become a proxy for clinical trials evidence.

Read the draft guidance here: www.fdanews.com/05-08-19-FDAGuidance.pdf. — Bill Myers

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Testing, *from Page 3*

Test report summaries should include the following elements:

- Identification of the tests performed;
- The objectives of the tests;
- A brief description of the test methods, including sample size, device tests and any consensus standards used;
- Predefined pass/fail criteria;
- A summary of results; and
- A discussion of the conclusions.

The complete test reports would include the above information as well as a data analysis plan with information on sample size and selection and any protocol deviations.

"A complete test report means the entirety of the testing documentation submitted for a study, which some submitters or test labs might embody in a single document, while others might embody in multiple and separate documents," the agency says.

In a written comment on the draft guidance, Cook Medical noted confusion around what items should be addressed by sponsors in their design files and regulatory submissions.

Cook urged the agency to maintain a distinction between the responsibilities of sponsors and the responsibilities of testing labs. The guidance "does not appear to recognize that sponsors frequently contract non-clinical testing to third-party laboratories who write testing reports," Cook said. Even when testing is performed by the sponsor's internal laboratories, the FDA and other global regulators often request procedures for managing potential bias or conflict of interest, the company said.

Read the final guidance here: www.fdanews.com/05-09-19-Performancetesting.pdf.

Surgisil Warned for Unapproved Marketing of Facial Implant

Plano, Texas devicemaker Surgisil is in hot water with the FDA over its Perma Facial Implant, a device that is only cleared for cosmetic facial augmentation and augmentations in areas like the nose, chin and cheeks.

The agency sent a warning letter after a September 2018 inspection, flagging the marketing of the implant for an unapproved use. The agency said the device was "intended to be implanted during surgery of the chin, jaw, nose, or bones or tissue near the eye or ear," but the company was marketing its Permalip implant for lip augmentation.

Lip augmentation "constitutes a major change/modification to its intended use" for which the firm lacked approval, the agency said. It warned that use of the PermaLip Implant in lip augmentation could cause the device to shift out of place or protrude due to the lips' anatomical and physiological differences from the nose, cheeks and skin, warning that infections, chronic pain and the need for surgical removal could follow.

The agency's investigators examined the company's instructional videos and marketing materials on its website, finding that they misled patients into believing the device could be used for the unapproved use. For example, the firm's three-minute facial implant instructional video covered the use of the facial implant in lip augmentation.

The agency also flagged a 12-item surgical checklist that instructed surgeons on using the facial implant, included a procedure for lip augmentation.

The FDA noted that the firm's website stated the implant is an "FDA approved device" and requested that it remove the false claim.

"The PermaLip Implant is not cleared or approved by FDA for marketing in the United States," the agency said. "Our office requests that your firm immediately cease activities that result in the misbranding or adulteration of the Permalip Implant, such as the commercial distribution of the device for the uses discussed above."

Read the Surgisil warning letter here: www.fdanews.com/05-09-19-Surgisil.pdf.
— James Miessler

Personnel Requirements for CAPAs

Companies putting together CAPA teams need to assign the following individuals:

- **CAPA manager:** This is the person in the company who is responsible for the overall CAPA system, including coordinating all CAPA activities and taking a role in investigations of nonconformances and other quality problems;
- **Process owner:** For each of the processes and data elements/sources that the company tracks, the company will need a process owner. Having process owners from the departments that actually conduct those processes will improve the quality of the data received and increase buy in to the CAPA process. This is important because one of the keys to CAPA success is breaking down "silos" and expanding participation beyond the quality team using a collaborative, cross-functional approach. The company should set regular planning, strategy and review meetings involving owners, team members and management;
- **CAPA owner:** Once a nonconformity or other problem is found, the company must assign it to a CAPA owner. This person will be responsible for coordinating a team to investigate the problem and then develop and implement a plan to correct the problem and prevent it from recurring; and
- **CAPA monitor:** The company should designate someone, such as the CAPA owner, to use trending techniques to catch—and address—quality problems early and to monitor ongoing process performance and the effectiveness of the CAPA plan.

Excerpted from the FDAnews management report: *Creating QSR-Compliant CAPA Systems: A Practical Guide for Devicemakers*.

European Commission Clarifies What UDI Info Is Needed for Eudamed

The European Commission released new details on what datasets devicemakers should include in the Eudamed database for unique device identifiers under the new Medical Device Regulation and In Vitro Diagnostic Regulation.

The overriding principle for the database is that each UDI device identifier (DI) inherits the attributes of its linked Basic UDI-DI—the primary identifier of a device model and the main key for records in the UDI database that's referenced in certificates and EU declarations of conformity.

The UDI-DI is the unique numeric or alpha-numeric code specific to a model of device, and it is also used as the access key to information stored in the UDI database.

The device data requirements are listed for the Basic UDI-DI, the UDI-DI and the UDI-DI container and are broken down by mandatory requirements, mandatory requirements if applicable and optional requirements. For example, "mandatory if applicable" fields include additional information for implantable devices under the Basic UDI-DI requirements.

The Medical Device Coordination Group (MDCG), which is comprised of representatives from all EU member states, released three guidances in May that clarified devicemakers' responsibilities for implementing UDI systems under the new MDR. Along with guidance on the basic attributes for a device identifier, the group released information on the database and the architecture for the new UDI system (*IDDM*, May 7).

A separate MDCG guidance on medical device software clarified that only software that is commercially available on its own or that constitutes a device in itself is subject to UDI requirements under the EU MDR and IVDR regulations.

Read the device dataset document here: www.fdanews.com/05-09-19-UDIdevicedataset.pdf.

Read the in vitro diagnostic dataset document here: www.fdanews.com/05-09-19-UDIdiagnosticdataset.pdf.

Read the data dictionary here: www.fdanews.com/05-09-19-UDIDatadictionary.zip.

BRIEFS

FDA Issues Final Guidance On Q-Submission Program

The FDA released final guidance on the forms of meetings and feedback devicemakers can request for various submissions under the agency's Q-Submission program.

The guidance outlines the options available to drug sponsors seeking input from the FDA for investigational device exemption applications, premarket approval applications, humanitarian device exemption applications, De Novo requests, 510(k) submissions, clinical laboratory improvement amendments (CLIA) waivers, dual 510(k) and CLIA waiver by application submissions (duals), accessory classification requests and certain INDs and BLAs.

The agency said the guidance reflects agreed-upon changes related to scheduling pre-submission meetings and clarifies other elements of the Q-Submission program.

"Early interaction with FDA on planned nonclinical and clinical studies and careful consideration of FDA's feedback may improve the quality of subsequent submissions, shorten total review times, and facilitate the development process for new devices," the agency said.

Read the Q-Submission guidance here: www.fdanews.com/05-09-19-Q-Submission.pdf.

FDA Clears Up Performance Standards For Fluoroscopic Equipment

The FDA issued final guidance clarifying the performance standard requirements for certain fluoroscopic equipment, devices that use X-rays to capture real-time moving images of an object's interior.

The agency decided to offer more clarification on fluoroscopy equipment performance standards based on input from a public meeting on reducing unnecessary radiation exposure from medical imaging.

The guidance doesn't cover angiographic X-ray systems, as they are incapable of performing fluoroscopies.

Read the fluoroscopic equipment guidance here: www.fdanews.com/05-09-19-Fluoroscopic.pdf.

Natera Earns Breakthrough Device Designation for Tumor DNA Test

The FDA granted Natera breakthrough device designation for its Signatera product, a post-surgical test used for detecting and quantifying circulating tumor DNA (ctDNA) in a patient's blood.

The test is tailored individually to patients previously diagnosed with certain cancers based on the unique mutations found in their tumors. It is meant to be used in combination with certain drugs.

Clinical studies showed that the test can identify residual disease in non-small cell lung, bladder, breast and colorectal cancer patients up to two years earlier than standard imaging.

APPROVALS

FDA Clears Subcutaneous Remodulin Delivery System

The FDA granted United Therapeutics and DEKA 510(k) clearance for the RemUnity subcutaneous delivery system for Remodulin (treprostinil), a continuous pump therapy used to treat pulmonary arterial hypertension.

The lightweight pump controls the drug's flow rates without the use of a motor using acoustic volume sensing technology and a solid-state actuator. The pump has a service life of at least three years.

United Therapeutics and DEKA are also developing a version of the device that uses prefilled disposable cartridges.

Boston Scientific Gains FDA Nod for Venous Stent

Boston Scientific has earned the FDA's premarket approval for the Vici Venous Stent system, a device used for treating iliofemoral venous obstructive disease.

Venous obstructive disease occurs when blood flow in the pelvic veins is compressed or blocked by a blood clot.

(See **Approvals**, *Page 8)*

Approvals, *from Page 7*

The stent's approval was based on data from a multi-center trial with 170 patients. The VIRTUS study met its primary safety and effectiveness endpoints.

The stent resists the compression encountered frequently in the iliofemoral venous system through its strong and crush resistant design and restores blood flow by creating a cylindrical vessel.

Medtronic's iPad-Based Pacemaker Programmer Receives FDA Clearance

The FDA has cleared Medtronic's CareLink SmartSync system, a pacemaker manager platform that programs and downloads data from cardiac implants using the Apple iPad.

The Bluetooth-capable system comes with a patient connector, telemetry head, base station and pacing system that weighs a little over two pounds when used with the iPad tablet.

The next-generation programmer and pacing system features encrypted data monitoring and is designed to replicate the interface of Medtronic's similar device, the CareLink 2090.

SentreHeart's Left Atrial Appendage Closure Device Gets CE Mark

SentreHeart earned the CE Mark for the 50mm version of its LARIAT-RS left atrial appendage (LAA) closure device.

Using imaging guidance, the LARIAT delivers a suture loop at the base of the LAA. Over time, the appendage disappear, so it is no longer a source of blood clots in patients with atrial fibrillation.

SentreHEART is conducting the aMAZE trial in up to 65 centers in the United States that seeks to show that the LARIAT procedure followed by a catheter ablation can reduce the incidence of recurrent atrial fibrillation.

The new 50mm device is now available in Europe along with the 45mm version.

Biofourmis' ECG Monitor Cleared by FDA for Sensing Cardiac Arrhythmias

The FDA granted 510(k) clearance for Biofourmis' RhythmAnalytics, an ECG monitoring device for detecting heart arrhythmias.

The monitor automatically analyzes heart arrhythmias and can detect 15 different types, including ventricular arrhythmias, ventricular ectopic beats and atrial fibrillation.

The device uses artificial intelligence models formed using over a million ECG recordings from multiple wearable monitors approved by the FDA.

FDA Approves Medtronic's Left Heart Lead

The FDA has given the green light for Medtronic's Attain Stability Quad MRI SureScan, a left heart lead device designed to be used with the company's defibrillators and pacemakers.

The device allows physicians to place the lead accurately in veins of various sizes, including ones in which positioning is difficult.

The lead enables physicians to "target the ideal location in the patient's vessel with the confidence that the lead will remain in place to allow for continued effective delivery of cardiac resynchronization therapy," said Steven Zweibel, director of electrophysiology at the Hartford Healthcare Heart and Vascular Institute.

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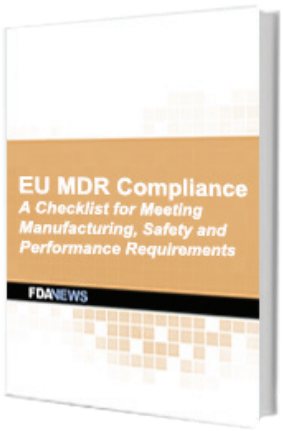

EU MDR Compliance: *A Checklist for Meeting Manufacturing, Safety and Performance Requirements*

The new EU Medical Device Regulation is massive… complex… and confusing… and you must be ready to comply by May 26, 2020.

When the European Union revised its system of rules for medical device manufacturers in 2017, it replaced a longstanding set of directives on specific topics with one large document that covers all aspects of making devices in EU countries.

Not only did they consolidate all the rules, they gave them greater weight. Previously, medical device directives provided guidance but did not have the force of law. The new MDR, however, contains mandates that are legally enforceable by EU member countries.

The FDAnews report **EU MDR Compliance** can help. Our editors have combed through the regulations, picking out the most minute compliance points and building them into a checklist of 200+ requirements you can use to confirm that you are satisfying all the EU mandates for device manufacturing. The report provides:

- Definitions of key terms in the EU MDR
- Knowing where to find specific requirements in the 150+ page regulation
- Checklists that walk you through every aspect of manufacturing, safety and performance requirements
- A training tool for employees new to the regulations

EU MDR Compliance: *A Checklist for Meeting Manufacturing, Safety and Performance Requirements* is the tool that collects all the requirements, explains them and itemized them in an easy-to-use form to ensure compliance.

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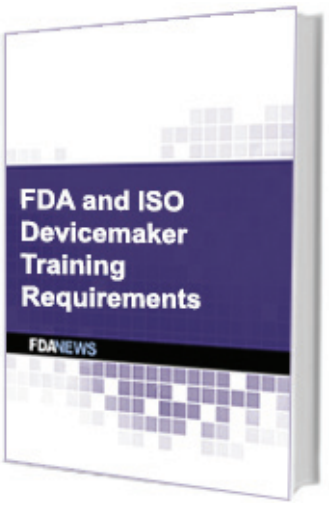

FDA and ISO Devicemaker Training Requirements

Device manufacture is a complicated business, but few areas are more rulebound than QMS. Many a devicemaker has come up short trying to stay abreast of the FDA's QSR, ISO 13485:2016, and other ISOs while trying to comply with competence, training and awareness rules.

It takes more than teaching simple skills to achieve the state of job readiness and performance required of devicemakers' workforces. Regulators agree that a comprehensive training program should consider employee education, experience, background and skills. What they don't agree on is what those concepts mean and how to incorporate them into training.

FDA and ISO Devicemaker Training Requirements breaks down training requirements in both the FDA's QSR and international standards ISO 13485, 9001 and 10018 — among others — shows where they overlap and where they differ and provides a plan for developing a training program that fills in all the gaps. You will learn:

- The four elements of competency
- Definitions of key terms and requirements
- The concept of a "designated individual" and the qualifications for the role
- The importance of a well-written job description
- The difference between a "job" and a "role"
- Factors in employee awareness and how to foster them
- How to evaluate your training program for compliance and effectiveness

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