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FDA Updates Investigational Device Guidance for CMS Coverage Decisions

The FDA is updating its policy on how medical devices with approved investigational device exemptions are categorized to help the Centers for Medicare and Medicaid Services make health insurance coverage decisions for Medicare beneficiaries.

The agency issued final guidance explaining the new framework CDRH and CBER will use when assigning IDE devices to one of two categories prior to clinical studies – Category A: Experimental and Category B: Nonexperimental/investigational.

The final guidance closely resembles the June 2016 draft version with some additional information on switching from Category B to A. It also includes new examples of data that can be used to support a category change.

CMS uses the categories to determine whether Medicare coverage requirements described in the Social Security Act are met. The Act states a device "must be reasonable and necessary for the diagnosis or

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

EU Releases Long-Awaited Designation Codes For Notified Bodies

The European Union Notified Bodies Operations Group released long-awaited codes for medical devices and in vitro diagnostics that correspond with the new EU regulations.

Conformity assessment bodies will need to use the new codes when submitting applications to become notified bodies (NBs). The codes define the scope of medical products that are covered, including medical devices and IVDs, so that manufacturers can determine which notified bodies to contact for conformity assessments.

It has been critical to get the list published quickly as the application process to become a NB went live on November 27. "These codes have been long-awaited, as they form the basis of the notified

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body designation under the new EU MDR and EU IVDR," Gert Bos, executive director at medical device regulatory consulting firm QServe Group, told FDAnews.

Bos, who previously served as a representative of European NBs, noted that "the system is the same as the currently used system, but as there is no grandfathering, all notified bodies have to apply from scratch again." It is also possible for a certain scope under the current Medical Device Directive to change under the future MDR, he said.

The application for NBs includes a specification of the conformity assessment activities and types of devices covered by the designation using the new codes. Devicemakers should be aware that there are some important differences with the new codes.

One important change is that the coding system is now published on the website of the European Commission. "In the past, it was only available on the private website of the NBOG, so the status has become more formal," Bos said. According to Bos, the coding system is now seen as legislation rather than as guidance.

Another difference Bos noted relate to the codes for medical devices, which are "similar to the current system, but presented in different order, and with a bit more detail." Special codes were added to service new types of products, such as non-medical implants.

The larger change is in the IVDR. The new classification is quite different from the current system, and the amount and spread of codes have substantially increased, Bos said, adding that more questions are asked about what materials are being used to produce certain products, such as metal or plastics.

A notified body with a full scope currently would be covering most of the new codes. But the issue would be whether the staff has the specific expertise needed for the dedicated codes.

Understanding which NBs have applied for what codes as well as "who will actually get the codes assigned in their designation" will be crucial, Bos said. "For some codes there will be many, for others only a few notified bodies, so if your product falls under such a code, it might be a challenge to find the notified body that can support the MDR review."

Read the NBOG documents here: www.fdanews.com/12-06-17-EUnotifiedbodies.pdf.

Guidance, *from Page 1*

treatment of an illness or injury, or to improve the functioning of a malformed body member."

Both agencies initially agreed on IDE reimbursement categorization in a September 1995 Interagency Agreement. But more than 20 years have passed, the FDA noted, and a lot has changed since then, prompting a 2015 Memorandum of Understanding.

Changes to the 1995 policy for categorizing IDE devices were needed because a number of IDEs did not easily fit into any of the eight subcategories identified in the agreement, which also lacked a description of a pathway for category changes.

The previous policy also "did not adequately articulate categorization criteria that are relevant to certain feasibility studies, particularly those for devices similar to approved devices but with modifications which raise significant new safety questions," the agency said.

Following approval of an IDE, the FDA will determine whether a device meets one or more of three criteria, which differ between the two categories, to make categorization decisions.

The agency also tweaked the draft guidance to note in the final version that "it is at the sponsor's discretion to communicate to CMS when IDE categorization changes" and that a change "for a given device will not automatically apply to similar devices."

Read the final guidance here: www.fdanews.com/12-05-17-CoverageDecisions.pdf.
— Ana Mulero

FDA Details Initial Thoughts On 3D-Printed Medical Devices

The FDA finalized a more detailed "leapfrog guidance" on additive manufactured, or 3D-printed, medical technologies, outlining its latest thinking on technical considerations.

From Stryker's FDA clearance of its 3D-printed titanium interbody fusion cage to the first surgery performed in the U.S. with a 3D-printed implant manufactured by Australian devicemaker Anatomics, 3D-printing has continued to gain momentum in recent months.

The FDA has approved marketing applications for more than 100 3D-printed medical devices and this is "likely just the tip of the iceberg given the exponential growth of innovative research in this field," said FDA Commissioner Scott Gottlieb.

Regulatory Pathway

According to Gottlieb, the agency is now preparing for "a significant wave of new technologies that are nearly certain to transform medical practice," and it is working to provide a more comprehensive regulatory pathway that keeps pace with the advances.

In the future, Gottlieb envisions the technology being used for 3D-printing new skin cells directly onto patients' burn wounds or for the development of replacement organs.

The guidance, which is organized into two broad sections — Design and Manufacturing Considerations (Section V) and Device Testing Considerations (Section VI) — can be used by manufacturers of devices with "at least one additively manufactured component or additively fabricated step" throughout the design development, production, process validation, and testing phases, the document states.

It is intended to help manufacturers bring their innovations to market more efficiently by providing a transparent process for future premarket submissions and "making sure our regulatory approach is properly tailored to the unique opportunities and challenges posed by this promising new technology," Gottlieb said.

It is categorized as "leapfrog guidance" because the manufacturing approach is still relatively new for emerging medical technologies, and the agency believes its recommendations are likely to evolve as the technology develops in unexpected ways.

The draft version, issued in May 2016, was substantially changed to reflect industry feedback.

The changes include additional details and sections, such as a new section on cybersecurity and personally identifiable information. In comments to the agency on the draft version, Johnson & Johnson expressed concerns about excluding this information, so the final guidance points to separate, previously issued HHS guidance on protecting protected health information.

Recommendations Tweaked

The wording used for some recommendations also was changed. As requested by AdvaMed, the agency tweaked its recommendation on verifying final products' attributes to strike the part about simulating-worst case scenarios to ensure these perform as expected and replaced it with: "…verify the critical attributes and performance criteria of your final products as part of the software workflow validation to ensure expected performance, especially for patient-matched devices."

AdvaMed had argued that "worst-case scenarios for patient-matched devices are impossible to determine because of the information received and subjectivity of worst-case determinations."

There is also new information on maintaining data integrity while handling complex design files.

It cautioned, however, that "not all considerations described will be applicable to every device, given the variety of AM technologies, materials and devices made with additive manufacturing."

Device manufacturers should make their own determinations on which considerations are appropriate for their specific device, the agency said.

Read the full guidance here: www.fdanews.com/12-05-17-AdditiveManufacturedMD.pdf.
— Ana Mulero

New FDA Guidance Narrows Agency Oversight of Digital Health Products

The FDA published three new guidances on digital health products that limit the types of products the agency will regulate as medical devices.

A draft guidance on clinical decision support software describes the types of software that will no longer be classified as medical devices, putting them beyond the agency's purview.

The Cures Act makes clear that certain digital health technologies—such as clinical administrative support software and mobile apps that are intended only for maintaining or encouraging a healthy lifestyle—generally fall outside the scope of FDA regulation, FDA Commissioner Scott Gottlieb told lawmakers in a December 7 hearing on Capitol Hill.

Software that will continue to fall under the FDA umbrella includes products whose primary function is processing in vitro diagnostic device signals, medical images and patterns acquired from processors.

In a separate draft guidance, the FDA proposed changes to existing guidance documents to better align them with the Cures Act's provisions. The guidance would establish that mobile apps aimed at improving lifestyle health generally, such as Fitbit and other step trackers, are not subject to FDA regulations.

The agency also issued a final guidance outlining steps required to generate clinical evidence of effectiveness and safety of software as a medical device (SaMD), developed in collaboration with the International Medical Device Regulators Forum.

The final version expands on the initial draft to establish common standards for evaluating safety and efficacy for software as a medical device, including globally recognized assessment principles, such as clinical evaluation processes, use of existing evidence and analytical validation.

Read the three guidance documents here: www.fdanews.com/12-07-17-Guidances.pdf.
— Zack Budryk

483 Roundup: Devicemakers Cited Over CAPAs, Other Violations

The FDA flagged five devicemakers for a variety of noncompliances observed during inspections, including inadequate CAPA procedures, and failure to properly investigate complaints.

Brit Systems: The FDA issued a Form 483 to Brit Systems in Dallas, Texas following an inspection in late August. The agency said the company's CAPA procedures were inadequate as they did not include requirements for verifying or validating a corrective or preventative action.

The agency also cited the facility for failing to have written procedures for managing medical device reportable events and for having a complaint handling procedure that did not evaluate MDR complaints.

Azena Medical: The FDA cited Azena Medical's facility in Walnut Creek, California, following an October inspection. The company failed to properly investigate complaints regarding the possible failure of its product Gemini Soft Tissue Laser to meet specifications. One complaint stated the product's tips had broken off, and a review of the complaint file revealed there was no documented investigation.

The company was also cited for its design change control procedure, which did not require the validation or verification of design changes before their implementation.

IanTech: IanTech's Reno, Nevada, facility was cited for failing to set up procedures for controlling and distributing finished devices. Prior to shipping the finished product, the firm failed to establish a quality system that met regulatory requirements.

The firm also had a controlled environment room classified as an ISO Class 8 cleanroom that was used in the manufacturing of a sterile finished device. When asked for qualification records, the firm provided validation result records but could not provide documented proof of validation activities. In addition, the controlled environment room's qualification result records showed the cleanroom was qualified only after the finished device was manufactured.

The FDA also cited the company for using software in its quality system that had not been

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Creating Compliant CAPA Systems

The first step in building a CAPA system is taking an inventory of the processes and data elements involved in manufacturing your products.

The FDA regulation that deals expressly with CAPA is CFR 21 Part 820.100 — Corrective and Preventive Action for devices.

The regulations identify specific minimum quality data that must be reviewed. These data include: processes, work operations, concessions, quality audit reports, quality records, service records, complaints and returned products.

When choosing specific quality measures to monitor as part of the CAPA system, it is important to adopt the perspective that you are selecting data points that will identify deviations or problems, not just all available data, said Deborah Lydick, president of Catalyst Advantage Group. Management needs to be closely involved to ensure that the correct elements of each process are measured.

"Obviously, understanding the indicators of your product and process performance is important to ensuring the effectiveness of your quality system," Lydick said. "It also helps you understand the interrelationship across the process and across data elements."

Complaints hold special status for the FDA and typically concern products already on the market. Companies must be aware that the FDA expects complaints to trigger a CAPA investigation. If three defective products make it into the marketplace, expect the FDA to take action, and failure to trend complaints will be a violation the FDA will cite a company for in a 483.

Excerpted from the FDAnews book: *Creating QSR-Compliant CAPA Systems: A practical Guide for Devicemakers*.

Devicemakers in Puerto Rico Draw Ongoing FDA Attention

The FDA remains seriously concerned about shortages of certain medical products as manufacturers in Puerto Rico continue their slow recovery from Hurricane Maria, but the shortage of IV saline products should improve by the end of the year, Commissioner Scott Gottlieb said in his latest update.

The agency is working with Baxter to address the shortage of IV saline products by helping to stabilizing production in its Puerto Rican facilities, and it approved IV solution products manufactured by Fresenius Kabi and Laboratorios Grifols (*IDDM*, Nov. 27).

It is also helping Baxter, one of the largest manufacturers of amino acids in the U.S. market, to temporarily import its amino acids for formulating IVs from its facilities in the United Kingdom and Italy, Gottlieb said. "Like with saline, an ongoing amino acid short supply situation was worsened by Hurricane Maria's impact on Puerto Rican drug manufacturing facilities," he said.

In addition, other manufacturers of the amino acids are working with the FDA to increase supplies. These include B. Braun and ICU Medical, which plans a return to the U.S. market in the near future after experiencing manufacturing delays.

The FDA is now monitoring about 90 medical products, including devices, biologics, and drugs, that are manufactured in Puerto Rico and are critical to patient health, he said.

This is a substantially higher than the number (30) he cited in an Oct. 24 hearing of the House Energy and Commerce Committee. At that time, no Puerto Rico medical product manufacturing facility had reached 70 percent of its pre-storm capacity, according to Gottlieb.

"Mitigating medical product shortages will require a sustained effort by industry, the agency and other partners as we work with manufacturers to return to production levels that adequately meet the needs of patients," he said. — Ana Mulero

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validated for its intended use. The firm used the software for document control as well as for SOPs, quality forms, nonconforming material records, CAPA records, complaint records, internal audit records, and other records.

LZR7: LZR7 in Placerville, California, drew a Form 483 following an October inspection, observing its MDR procedures failed to not address numerous issues.

The procedures did not establish a standardized review process for determining when an event should be reported, and did not allow the timely transmission of complete medical device reports to the FDA. The procedures also did not establish internal systems that would allow efficient and effective analysis of events that might be subject to MDR requirements, the agency said.

AccessClosure: The AccessClosure facility in Santa Clara, California received a Form 483 because it did not satisfactorily establish procedures for handling complaints.

After reviewing the firm's complaint files, inspectors found that the patient, device and event detail information was not adequately collected, and devices were not gathered for examination. No documentation was found indicating that the firm followed up to obtain missing or additional information or issued a device recall that would have aided in the investigation.

Read the Brit Systems Form 483 here: www.fdanews.com/12-06-17-britsystems483.pdf.

Read the Azena Medical Form 483 here: www.fdanews.com/12-06-17-azenamedicalllc483.pdf.

Read the IanTech Form 483 here: www.fdanews.com/12-06-17-iantechinc483.pdf.

Read the LZR7 Form 483 here: www.fdanews.com/12-06-17-lzr7inc483.pdf.

Read the AccessClosure Form 483 here: www.fdanews.com/12-06-17-accessclosure483.pdf. — James Miessler

FDA Warns Hand Biomechanics Over MDR, GMP Issues

Hand Biomechanics Lab, a manufacturer of bone fixation fastener systems in Sacramento, California, was hit with an FDA warning letter for failing to submit MDRs and for GMP nonconformities.

The firm's procedure for MDR submissions lacked definitions for terms such as "become aware," "caused or contributed," and "MDR reportable event" that may have caused it to make inappropriate decisions when evaluating complaints. It was also flagged for incomplete investigations and for not providing timely MDR submissions.

The firm failed to submit MDRs after it received at least three complaints regarding patients who required prescription antibiotics for pin site infections developed while being treated with the Digit Widget device, and another complaint about a patient having the device surgically removed due to the infection sustained with use.

The firm did not submit MDRs to the agency for these complaints and others, according to the warning letter, even though they describe events in which "medical intervention was necessitated to preclude permanent impairment of a body function or permanent damage to a body structure."

The GMP nonconformities that resulted in adulterated devices relate to failing to demonstrate the sealing process could produce "repeatable and reproducible seals capable of maintaining seal integrity throughout the shelf-life of the product" and evaluating defects.

In addition, at least 10 CAPA records between Feb. 24, 2015 and Feb. 3, 2017 lacked investigations, corrective actions or preventive actions, the FDA said.

Read the warning letter here: www.fdanews.com/12-05-17-HandBiomechanicsLab.pdf.
— Ana Mulero

APPROVALS

FDA Clears Perspectum Diagnostics Liver Scanning Device

The FDA granted marketing clearance to Perspectum Diagnostics' Liver*MultiScan* a post-processing software device for magnetic resonance imaging of the liver, delivered through a cloud-based service.

The liver characterization procedure is non-invasive and does not require contrast agents. The clearance means the technology can now be used on a wider range of scanners, including compatible Siemens and Philips MR systems.

The device is CE marked in Europe.

Aidoc Gets CE Mark for Deep Learning Imaging Solution

Artificial intelligence startup Aidoc earned a CE Mark for its head and neck deep learning medical imaging solution.

The device is designed to improve radiologists' workflows by detecting abnormalities in imaging to aid in more timely diagnoses. The technology allows radiologists to prioritize cases based on AI medical image analysis in conjunction with other clinically available data.

Cagent Vascular Receives CE Mark For Vessel Dilatation Device

Cagent Vascular earned a CE Mark for its Serranator PTA serration balloon catheter.

The product features four serrated metal strips that help improve arterial expansion.

The Serranator "capitalizes on the simplicity and familiarity of angioplasty while introducing a new and more effective method of vessel expansion," said Cagent's co-founder and chief medical officer, Peter Schneider.

Cagent received FDA Clearance for its first product, Serranator Alto, early this year.

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Approvals, *from Page 7*

Cerebrotech Wins CE Mark For Intracranial Fluids Monitor

California-based Cerebrotech Medical Systems has received CE Mark for its Intracranial Fluids Monitor powered by proprietary machine learning and artificial intelligence software.

The non-invasive bioimpedance spectroscopy device is designed for detecting changes in and the distribution of brain fluids to identify signals associated with stroke in less than one minute. The company has plans to also train the device's software to detect a range of health-related complications, including traumatic brain injury and brain tumors.

South Africa Approves United Health Products' HemoStyp Device

United Health Products received regulatory approval to market its patented hemostatic gauze in South Africa.

HemoStyp is indicated for treating wounds that have breached the skin's dermis, including chronic extensive ulcerated wounds and severe burns, the company said.

Omega Diagnostics HIV Test Scores CE Mark

UK-based Omega Diagnostics Group earned a CE Mark for its VISITECT CD4 HIV test.

The disposable test is designed to determine immune status of patients diagnosed with the HIV infection with whole blood samples.

An optional reader is available for clinics and laboratories requiring full traceability, positive patient ID and storage of patient results.

The company said it will seek additional regulatory approval through the World Health Organization Prequalification Programme.

AliveCor Receives FDA Clearance for First Apple Watch Medical Device Accessory

The FDA cleared the first medical device accessory for the Apple Watch, manufactured by California-based developer of personal electrocardiogram (EKG) technology AliveCor.

KardiaBand can record an EKG in 30 seconds and detect normal sinus heart rhythms as well as atrial fibrillation, the most common heart arrhythmia.

The product requires a subscription from AliveCor for use with the Apple Watch. The app features the company's SmartRhythm, which can continuously monitor the correlation between users' heart and physical activity, to notify them when an EKG should be captured.

FDA Approves NGS-based IVD Test With Breakthrough Designation

The FDA approved the first next generation sequencing (NGS)-based in vitro diagnostic test with breakthrough designation, FoundationOne CDx (F1CDx).

The IVD test from Roche's Foundation Medicine is the second to be approved under the FDA/CMS Parallel Review Program, in which the FDA collaborates with the Centers for Medicare and Medicaid Services to expedite the review process, so Medicare beneficiaries have earlier access to innovative medical technologies.

The F1CDx can detect mutations in 324 genes and two genomic signatures by sequencing DNA.

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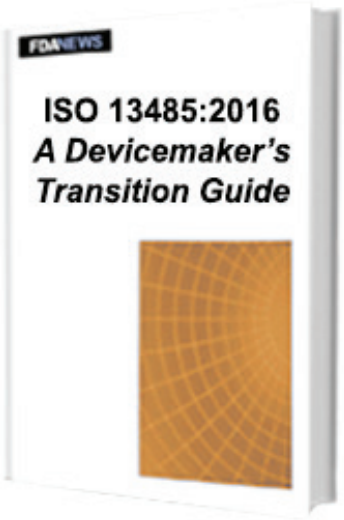

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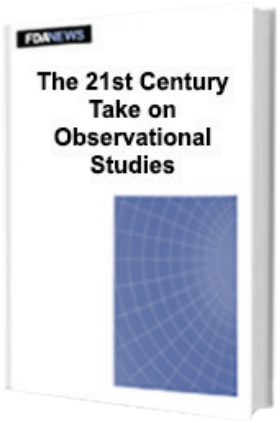

The 21st Century Take on Observational Studies: *Using Real-World Evidence in the New Millennium*

Passage of the 21st Century Cures Act reaffirmed Congress's and the FDA's commitment to using real-world evidence to supplement or even replace traditional clinical trials.

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