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IN THIS ISSUE

FDA Suggests Alternatives For Complying With QS Requirements

The FDA put out a list of alternative ways to comply with quality system requirements for device combination products, making suggestions for design controls and quality system regulation exemptions.

Combination product manufacturers can use existing pharmaceutical development practices and documentation that align with the 21st Century Cures Act's requirements and design control principles for meeting device QS regulations, the agency said.

"Particular attention should be given to postmarket management of design changes to the combination product and the alignment of change control practices with the principles and requirements" when assessing the suitability of pharmaceutical development processes that are already established, the agency said.

The combination product can also be exempted from certain — and in some cases all — device QS requirements if the device constituent that is part of the combination product is exempt from such

(See **Requirements**, *Page 2)*

House Bill Would Streamline CMS Process for Breakthrough Technologies

Devicemakers would see new devices or diagnostics designated as breakthrough technologies receive immediate coverage by the Centers for Medicare & Medicaid Services for three years under new legislation introduced in Congress.

Currently, Medicare does not automatically cover the latest advances in medical technology. The lag between FDA approval and Medicare's coverage determination can take up to three years.

The Ensuring Patient Access to Critical Breakthrough Products Act (H.R. 5997) would require Medicare to cover all breakthrough products that are approved through the FDA's expedited review process for three years. Within those three years Medicare must make a permanent coverage determination.

(See **CMS**, *Page 2)*

Requirements, *from Page 1*

requirements and use of the part is within the scope of the exemption.

"We interpret this exemption to mean that the use of the device in the combination product must not be a new intended use or otherwise raise different safety and effectiveness questions for the device," the agency said.

The exemption will most frequently be applied to co-packaged combination products, the FDA said. For example, exemption from certain device QS regulation requirements may apply to an oral dosing syringe co-packaged with a drug. However, packaging the dispenser into a primary container closure system or co-packaging the dispenser with an emergency-use product could create a new intended use or raise safety concerns and void the exemption.

The agency requested comments on the list by Sept. 11, 2018.

Read the proposed list here: www.fdanews.com/06-13-18-GMPComboProducts.pdf.
— James Miessler

CMS, *from Page 1*

AdvaMed welcomed the proposed legislation, saying "American patients deserve better," and the legislation introduced by Reps. Suzan DelBene (D-Wash.), Jackie Walorski (R-Ind.), Tony Cardenas (D-Calif.), Gus Bilirakis (R-Fla.) and Terri Sewell (D-Ala.) will "help ensure they get better."

In addition, the legislation would make improvements to CMS's New Technology Add-on Payment (NTAP) program to reduce disincentives that limit prompt patient access to innovative technologies.

"Taken together, the breakthrough policy proposal and NTAP reforms would both stimulate development of important new devices and diagnostics and assure more rapid availability of those treatment options to patients," the association said.

For a medical device to earn the "breakthrough" designation, the new technology must:

- Provide more effective treatment or diagnosis of life-threatening or irreversibly debilitating diseases or conditions;
- Have no approved alternatives;
- Offer significant advantages over existing approved alternatives; or
- Availability is in the best interest of patients.

"It makes no sense that Medicare drags its- feet to cover cutting edge technologies, especially when the FDA works to expedite their own review process for these same treatments," Rep. DelBene said. "The guaranteed coverage of these breakthrough technologies will also foster investment in the industry which will yield greater advances in the future."

"We must ensure that the review and approval process for breakthrough therapies doesn't inhibit patient access to the most innovative and effective technologies coming to market," said Rep. Sewell, adding that the legislation is a step toward "streamlining the regulatory process and ensuring that these devices reach the patients who need them in a timely manner."

There are more than 600 medical device companies in Florida working to develop innovative and effective products, said Rep. Bilirakis, noting that during a roundtable discussion in his district, device manufacturers expressed frustration over lengthy Medicare coverage delays that create barriers in bringing new products to market.

"Government has to get out of the way and streamline the payment process for effective new devices that can ultimately help improve and save lives," he said.

TGA to Lift Extra Scrutiny Of EU Device Notified Bodies

Australia's Therapeutic Goods Administration will loosen its oversight of certain notified bodies, the agency announced last week.

The move comes after a TGA assessment decided increased oversight of the bodies in the European Union had satisfied earlier concerns about the dependability of assessments for medical devices.

The TGA implemented the heightened scrutiny in 2014 for eight European institutions after a *British Medical Journal* investigation indicated the bodies had based decisions on minimal evidence of safety and efficacy for high-risk devices.

Based on the EU's reforms, the agency decided to reduce its scrutiny. The EU de-designated some of the notified bodies while redefining the designations of others.

"As a result of the added scrutiny of notified bodies that has recently occurred in Europe … the TGA no longer considers it necessary to apply these increased audit requirements," the agency said.

FDA Clarifies Post-Cures Act Humanitarian Device Exemptions

As mandated in the 21st Century Cures Act, the FDA issued draft guidance to clarify the agency's rules on humanitarian device exemptions under the act.

The FDA said it will consider the target patient population, size, intended use and current treatment options in assessing devices for the HDE program.

To qualify for the program, devices should be intended for treatment or diagnosis of conditions affecting a maximum of the Cures Act's limit of 8,000 U.S. patients.

The guidance also explains distinctions between the FDA's review of HDE applications and the premarket approval application program. For example, HDE applications are not subject to user fees, and accepted applications without any major amendments are reviewed in 75 days, compared to 180 days for PMA applications.

Under the 2017 FDA Reauthorization Act, an institutional review board or "appropriate local committee" can issue an approval. A local committee qualifies if it is a standing facility committee that has "expertise and experience in reviewing and making treatment decisions for clinical care, particularly in applying innovative medical device technologies to clinical care," according to the draft.

Read the draft guidance here: www.fdanews.com/06-14-18-HDE.pdf. — Zack Budryk

FDA Issues Recommendations On 510(k) Applications for Guidewires

The FDA released draft guidance with recommendations for 510(k) submissions of guidewires intended for use in coronary, peripheral and neurovasculature procedures, including recommendations for biocompatibility tests.

The guidance provides an example table with suggested information to include in a side-by-side comparison with a similar legally marketed predicate device, such as tip material, shelf life, indications for use, device length, wire diameter and wire material.

Because guidewires contain materials that come in contact with patients and could produce a harmful effect, the FDA recommends that all patient-contacting materials in the device undergo a biocompatibility determination.

Previous testing experience or documentation of guidewires with a history of success may be included when appropriate if the device's composition and processing methods are identical.

A biocompatibility risk assessment should be conducted if the manufacturer cannot identify a legally marketed predicate device with a similar intended use and location/duration of contact that uses the same materials. The assessment should explain the relationship between the identified biocompatibility risks, the information available for mitigating them and any remaining knowledge gaps, the agency said.

(See **Guidewire***, Page 4)*

FDA Reports to Congress on 'Least Burdensome' Training for CDRH Staff

The FDA issued a report to Congress on the results of mandatory training given to its premarket device review staff on applying the least burdensome requirements in product reviews.

The mandatory training — which was required by the 21st Century Cures Act — instructed 1,148 CDRH and 267 CBER staff members on the implementation of least burdensome requirements, according to the audit report.

"The effort put in place to implement the Cures Act is resulting in improvements towards the appropriate application of the least burdensome concepts and principles," the agency said.

The FDA defined least burdensome to mean the "minimum amount of information necessary to adequately address a regulatory question or issue through the most efficient manner at the right time." The concept applies to all products that meet the statutory definition of a device and throughout the total product lifecycle, both pre and postmarket.

CDRH is anticipating requests for additional information as the premarket device review program implements the least burdensome provisions and as reviewers apply what they learn from training.

Read the FDA audit report here: www.fdanews.com/06-14-18-TrainingAudit.pdf. — James Miessler

TGA Issues New Fees for Devices

Starting July 1, devicemakers will pay new fees to Australia's Therapeutics Goods Administration to register their devices and in vitro diagnostics and to keep them on the Australian Register of Therapeutic Goods.

To register devices, manufacturers and sponsors will pay roughly A$1,000 (US$747) to apply to list their devices on the ARTG. Applicants seeking a priority review will pay A$9,840 ($7,350).

Manufacturers also will pay application audit fees that include conformity assessment application fees of A$7,030 ($5251) and fees of A$3,080 ($2,300) to verify the application and conformity assessment.

Surveillance inspections will cost manufacturers A$8,620, and additional inspection costs will be billed at the rate of A$420 per hour per assessor.

For IVDs, manufacturers will pay A$670 ($500) in annual charges and about A$1,000 in application fees. Applications for priority review are billed at the same rate as priority reviews for medical devices.

Guidewire, *from Page 3*

For determining the types of biocompatibility assessments to use, the FDA recommends referring to its guidance, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process.

When finalized, the guidance will supersede the agency's January 1995 Coronary and Cerebrovascular Guidewire Guidance.

Read the draft guidance here: www.fdanews.com/06-14-18-Guidewires.pdf. — James Miessler

FDA Hits Arcamed For CAPA, Training Issues

The FDA cited Arcamed for deficiencies in its CAPA procedures and issues with its quality audit and employee training procedures after a February/March inspection of the company's Indianapolis facility.

The investigators found that seven of 11 product nonconformances were marked "Use As Is," and the box for "CAPA Investigation" was marked "No" for all seven. None of the noncomforances included a scientific explanation for the final disposition.

The company also failed to follow its written procedures when verifying the effectiveness of its CAPAs, with eight of nine closed CAPA files lacking any objective evidence supporting their effectiveness. In six of nine closed CAPA files, the initiation form was not properly completed in compliance with the procedures.

The agency also found that the company did not use a supplier on its approved supplier list on several occasions, and it did not list a disqualified supplier on the appropriate section of its supplier list as required by company procedures.

The company's management confirmed it had no internal audit schedule for 2016 and 2017, as required by its internal quality audit procedure, and the only evidence that audits were conducted in 2016 indicated they were partial audits.

In addition, investigators found training records were incomplete for one of three employees reviewed, and did not include evidence of training in risk management and validation, calibration and quality control.

Read the Arcamed Form 483 here: www.fdanews.com/06-14-18-arcamedllc483.pdf.
— Zack Budryk

CAPA Trending

The FDA expects companies to identify trends while analyzing their quality data — and to act on what they learn. In other words, the FDA expects companies to do more than provide the agency a look back at data and an after-the-fact reaction to quality problems. Companies must use trending techniques to catch — and address — quality problems early.

Companies must review all data sources, even though information may be scattered in isolated "data silos" such as consumer complaint files and out-of-specification (OOS) reports. Sources must be scrutinized and analyzed using statistical tools in order to quickly spot trends, especially in quality control issues. The FDA wants companies to have established quality data systems, with controls for both the system and its content, including full validation of systems, processes and end products.

Timing is also important. Examination of data for trends needs to occur at least during each management review, but may be needed more frequently. The FDA is not specific on the frequency of data reviews, but the agency expects companies to analyze data for trends often enough that issues are caught in a timely manner.

Equally important is the response to issues identified through trending. FDA inspectors expect to see results, including escalation into a CAPA if necessary. Companies can employ log sheets to document each identified trend and the company's responses: CAPA, investigation, document change, specification update, etc.

Additionally, the procedure needs to define what constitutes a trend. Each company must establish "rules" or parameters. Generally, a single occurrence would be considered merely an incident, but if the average is much less than one, one occurrence could be considered a trend. The frequency of trending efforts — monthly, quarterly, etc. — must be specified. The procedure must also detail how identified trends will be documented.

Since the data being trended likely is housed in computer databases, these need to be validated and that validation needs to be documented.

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

Ohio Device Manufacturer Scolded for MDR Procedure, Complaint Handling

The FDA slapped Gendron with a Form 483 for shoddy complaint handling and deficient MDR procedures, as well as issues with its internal quality auditing.

The inspection, which was conducted in March, revealed that the company did not notify its regulatory designee, complaint handling unit or company president within a set amount of hours of receiving a potential reportable or MDR complaint. Specifically, no documentation existed to show that they were notified of the complaints.

The company also failed to review and investigate MDR reportable complaints and incorrectly assigned risk index levels to complaints, which are assigned by the firm's complaint handling unit.

Documentation also did not exist showing that the firm's complaint handling unit evaluated complaint logs for any potential reportable complaints and noted trends that warranted further review. The lack of documentation made the investigator unable to verify that complaint log reviews were being conducted.

In addition, the firm's internal quality audit procedure lacked requirements for necessary audits. For example, the firm did not audit all areas of its quality management system, such as medical device reporting and control of nonconforming material.

Gendron's purchasing control procedure also did not adequately define controls for suppliers. The procedure required suppliers to complete a vendor report card to determine if an on-site audit is required but did not specify the frequency of the assessment.

Read the Gendron Form 483 here: www.fdanews.com/06-15-18-gendroninc483.pdf. — James Miessler

FDA Offers Labeling Advice For Devices With Lubricious Coatings

The FDA released draft guidance offering recommendations for information to include in labeling for devices with lubricious coating, such as intravascular catheters, guidewires, delivery sheaths and implant delivery systems.

The guidance offers labeling recommendations for both Class II and Class III devices. Although some of its considerations could apply to devices with similar coatings used in other types of interventional procedures, the scope of the guidance focuses on devices used in the neuro, coronary and peripheral vasculature.

For those devices, the FDA recommends that the labeling include a statement identifying whether or not the device is coated. If it is coated, a brief description — such as noting if the coating is hydrophilic or hydrophobic, as well as its purpose and location on the device — is suggested.

Any indications for use described in the labeling should be supported by information in the device's premarket submission. For intravascular devices, any specific regions of the vasculature for which the device is cleared should be identified.

A general warning explaining that the device is coated should be inserted at the beginning of the labeling. The agency also recommends that the labeling note any other specific considerations, such as storage conditions, specific preparation steps or device compatibility, that the user should know about to improve safe use of the device.

Preparation steps should include information to guide the user in a clinical setting. Some of the items may be included as warnings or precautions in the instructions for use or on the outer label. The guidance includes a table of specific recommendations to consider when developing the labeling.

Adverse events that could be caused by coating loss, such as sterile inflammation, tissue necrosis, embolic stroke or pulmonary embolisms, should be explained in the labeling.

Read the draft guidance here: www.fdanews.com/06-15-18-Intravascular.pdf. — James Miessler

France to Beef Up Clinical Trial Requirements for Flow Diverter Stents

France's National Agency for the Safety of Medicines (ANSM) is calling for more exhaustive clinical studies prior to CE marking of flow diverter stents that are implanted to treat intracranial aneurysms.

ANSM said claims for equivalence with one or more devices of another brand in the CE marking process should not apply and said it would pursue stiffer regulations to strengthen evaluation criteria before CE marks are granted.

There are five CE marked flow diverter intracranial stents used to treat aneurysms: the Balt Extrusion's Silk stent, EV3's Pipeline Embolization Device, Stryker's Surpass Flow Diverter Stent, Microvention's Flow Re-Direction Endoluminal Device and Phenox's p64 stent.

ANSM said all the manufacturers are up to date with their regulatory obligations, but the quantity and quality of the available preclinical data was mixed, as some stents had full preclinical data, while others did not. Post-marketing clinical data was available for all five stents, but the data varied in terms of reporting morbidity and mortality as well as occlusion rates of aneurysms.

ANSM conducted inspections between April and November 2017 at four flow diverter stent manufacturers: Microvention, Stryker, Phenox and Medtronic. Those inspections did not raise particular concerns, the agency said.

APPROVALS

FDA Grants Expanded Approval for Intuitive Surgical's Robot-Assisted Surgery Device

Intuitive Surgical received 510(k) clearance for a new indication for its da Vinci SP robot-assisted surgery device.

The new indication is for urologic surgical procedures that require very narrow access from a small incision appropriate for a single port approach. The company plans to pursue additional clearances for other applications.

The system includes three multi-jointed wristed instruments and a fully wristed 3D HD camera. The system allows for flexible port placement and 360 degrees of anatomical access.

FDA Clears Insulet's Omnipod System

Tubeless insulin pump developer Insulet received 510(k) clearance for its Omnipod Dash insulin management system.

The Dash is optimized for use with the Contour Next One blood glucose meter to transfer blood glucose readings to the touch-screen personal diabetes manager.

The device uses Bluetooth to connect with the Omnipod Display and Omnipod View apps, giving users and caregivers access to their insulin therapy information on their smartphones.

Centinel Spine Gets Clearance For Interbody Fusion Device

The FDA granted Centinel Spine 510(k) clearance to market its FLX platform of integrated and non-integrated interbody fusion devices.

The 3D printed titanium devices feature porous radiolucent sections to reduce mechanical stiffness and improve visibility compared with solid titanium implants.

The devices also have a proprietary trabecular scaffold that allows for bony in-growth and on-growth throughout the implant. They are indicated for use at one or two contiguous levels with both autograft and/or allogenic bone graft.

FDA Clears EDAP TMS's Focal One

EDAP TMS received 510(k) clearance for its Focal One device, used for the surgical removal of prostate tissue.

The device uses high intensity focused ultrasound to ablate prostate tissue and combines the

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

Approvals, *from Page 7*

use of MR and 3D biopsy data with real-time ultrasound imaging.

Using the device, urology surgeons can define precise contours around diseased tissue and remove a smaller portion of the prostate, lessening damage to healthy tissue and minimizing side effects.

LivaNova Aortic Heart Valve Approved in Japan

Japan's Ministry of Health, Labor and Welfare approved LivaNova's sutureless aortic heart valve for treating aortic valve disease.

The device, known as the Perceval sutureless valve, is designed to lessen the physiological impact of aortic valve replacement. It received the FDA's approval in 2016.

The valve can be used in a variety of surgical methods, including traditional procedures and minimally invasive approaches.

K2M Group's Cervical Plate System Receives FDA Clearance

The FDA granted 510(k) clearance to K2M Group's Ozark cervical plate systems, designed for anterior screw fixation to the cervical spine in patients with deformity, tumor, trauma or degenerative disease.

The systems are available in two designs — the Ozark Guide and Ozark View — and both feature a locking cover that gives surgeons a clear view of the final lock position.

The devices offer a full range of plate and screw sizes and instrumentation for constrained, semi-constrained or hybrid screw constructs, and are compatible with K2M's Cascadia 3D interbody systems.

OrthoSensor Earns Further 510(k) Clearance

The FDA granted OrthoSensor, a developer of sensor-assisted devices for total knee replacement, additional 510(k) clearance for its Verasense assisted technology.

The device is designed to help patients who complain of stiffness, pain and loss in range of motion following total knee replacement surgeries.

The clearance allows the device to be used with Zimmer Biomet's Persona knee system for total knee replacement.

Icotec's Interbody Cages Cleared by FDA

The FDA granted marketing clearance for Icotec's BlackArmor interbody cages used for lumbar procedures.

The cages are designed to improve bony integration and post-operative visualization, and the clearance applies to a variety of surgical approaches including cervical and lumbar procedures.

The device's material consists of continuous carbon fibers combined with polyether ether ketone (PEEK), an organic thermoplastic polymer, allowing consistent orientation of the carbon fibers for strength and mechanical durability.

OptoVue Gets Clearance for Blood Vessel Measurement Device

Fremont, California based OptoVue received 510(k) clearance from the FDA for its AngioAnalytics optical coherence tomography angiography blood vessel measurement technology.

The device provides high-resolution imaging of retinal blood vessels and is designed to help manage diseases that cause progressive blindness.

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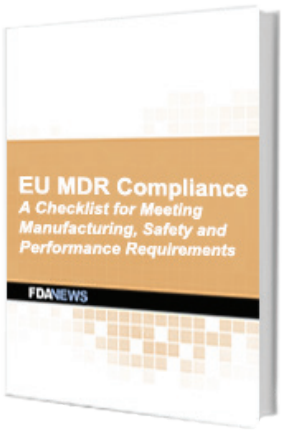

EU MDR Compliance: *A Checklist for Meeting Manufacturing, Safety and Performance Requirements*

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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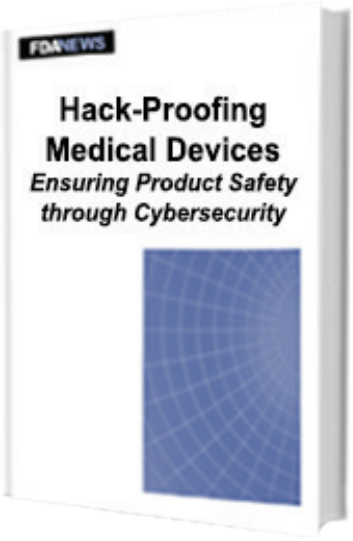

Hack-Proofing Medical Devices: *Ensuring Product Safety through Cybersecurity*

How does the FDA expect you to fight cyber incursions?

With the recent release of the final guidance on postmarket management of cybersecurity, you now have advice from the agency.

The key is awareness — of product vulnerabilities, current threats, developments in cybersecurity protection, how to defend your company from disastrous liability litigation… and the list goes on.

Hack-Proofing Medical Devices will show you how to get — and keep — control of your devices' networked operations. The management report covers:

- Six environmental stressors that contribute to cybersecurity problems
- The overwhelming magnitude of the problem — 68,000 medical devices were found to be freely accessible through the Internet in 2015
- How the FDA and international regulators are handling issues involving software as a medical device (SaMD)
- Types of cybersecurity threats, including ransomware and device piggybacking
- And much more!

BONUS — the report also provides a variety of tools including:

- A checklist for verifying a device's cybersecurity controls status
- A sample medical device cybersecurity policy
- Spreadsheets that help assess level and severity of risk

Order your copy of **Hack-Proofing Medical Devices** and understand the nature of cybersecurity threats, how and where they occur and what you can do to prevent outside interference.

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