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IN THIS ISSUE

FDA Releases Final Guidance On Benefit-Risk Factors for 510(k) Submissions

The FDA released a final guidance for 510(k) applicants on how to show substantial equivalence for devices with benefit-risk profiles that differ technologically from the devices on which they are based.

New devices don't need to have the same benefit-risk profiles as their predicate devices to be "substantially equivalent," the FDA said, but in those situations, a benefit-risk assessment should be made to determine if the new device is as safe and effective as its predicate version.

When comparing the benefits and risks of a new device to a predicate device, there might be variability in the type or extent of benefits and/or risks," the FDA said. When this happens, the agency evaluates benefit-risk differences. For benefits, the agency considers their type, magnitude, likelihood and duration. When assessing risks, it looks at their severity, types, number, probability and rates.

(See **510(k)**, *Page 2)*

India Releases Comprehensive Reference Manual on New Medical Device Rules

India's Ministry of Health & Family Welfare released a 241-page draft guidance to help devicemakers better understand the country's new device rules that came into effect in January.

Prepared by the Indian Pharmacopoeia Commission, the guidance covers regulatory requirements, quality management systems and standards and is intended to serve as a reference manual that will be updated as needed.

The guidance covers the device classification system, notified bodies and general requirements for good manufacturing practices. The classification of a device determines which agency regulates the device. For Class A and Class B devices, the State Drugs Controller serves as the State Licensing Authority, while higher-risk Class C and Class D devices are regulated by the Central Licensing Authority.

(See **India**, *Page 2)*

India, *from Page 1*

Manufacturers that don't have a manufacturing facility in India must have an authorized agent in India to submit an application for an import license. Once a license is granted, it is valid "in perpetuity" unless cancelled or surrendered, the guidance says.

For import licenses, a notarized copy of the overseas manufacturing site and free sale certificate are required along with a notarized copy of the full quality assurance certificate and a copy of the most recent inspection/audit report from a notified body.

Applicants may group medical devices having the same or similar intended uses "or commonality of technology" on a single application. But a single medical device sold as a distinct packaged entity does not meet the criteria for a cluster or a group and as such must be licensed separately.

The guidance clarifies the difference between a family of medical devices and which can be grouped together such as IVD test kits.

The guidance lists fees and charges. Import licenses range from $1,000 for one site for a Class A device, to $2,000 for one site for a Class B device, and $3,000 for one site for a Class C or Class D device. The fee for inspecting an overseas facility is $6,000. There are also additional fees for conducting clinical trials.

Devices require the following labeling information on the outside package of each device:

- Name of the medical device;
- Details to identify the device and its use;
- Name of the manufacturer and address of manufacturing facility where the device was manufactured;
- Net quantity in terms of weight, measure, volume, and number of units in the package (using the metric system); and
- Expiration date, and date of sterilization for sterile devices.

Unique device identifiers will be required in India beginning Jan. 1, 2022.

Devices intended for international distribution must conform to ISO standards. However, the guidance also lists Indian standards for various types of devices and notes that "while it may be preferable for harmonization purposes to use international standards, it may be appropriate for regulatory authorities to accept the use of national/regional standards."

Reed the draft guidance here: www.fdanews.com/09-25-18-GuidanceDocumentforMD.pdf.

510(k), *from Page 1*

The FDA may consider aspects of post-market data when reviewing a device — such as device literature, registry data, MDRs and any recalls — collected from marketed devices of the same type, in order to "clarify the magnitude and effect of mitigations" and gather more information when evaluating risks and benefits to determine substantial equivalency.

The agency also evaluates other factors, such as the extent of uncertainty, patient risk tolerance, characterization of the disease or condition, risk mitigation and post-market data.

The guidance makes no changes to the 510(k) premarket review standards or requirements and does not create any new regulatory requirements for applicants; it is just aimed at improving the "predictability, consistency and transparency" of the review process, the agency said.

Read the final guidance here: www.fdanews.com/09-27-18-PremarketNotifications.pdf.
— James Miessler

Devicemakers Critical of FDA Test Methods for Metal Biliary Stent PMAs

Boston Scientific and Cook Medical questioned parts of the FDA's guidance on premarket notifications for metal expandable biliary stents and their delivery systems — including limits on eligibility for the Special 510(k) program and some recommended test methods in the draft released in July.

When the original 1998 guidance was drafted, the FDA had concerns about biliary stents being used off-label for vascular systems, which could cause harm due to lack of safety and efficacy data. Metallic stents have since been approved for cardiovascular indications, but the agency still has concerns about use of the biliary stents for cardiovascular indications unless they have also been cleared for CV indications through a PMA.

In its comments on the guidance, Cook Medical challenged the language in the guidance that said "modifications to biliary stents are not eligible to be reviewed under the Special 510(k) program." Cook suggested that by not allowing biliary stents to be eligible for submission under the Special 510(k) paradigm that the agency is violating its own guiding principles detailed in Oct. 25, 2017 510(k) guidance that emphasized taking a least-burdensome approach.

Equivalence

"Selectively excluding a device from a well-established regulatory pathway sets a dangerous precedent," Cook Medical said.

The agency also continues to place limitations on substantial equivalence determinations for biliary stents and the guidance limits biliary stents indicated for palliation of malignant strictures in the biliary tree, the company said.

Cook Medical took issue with the FDA restricting the use of biliary stents indicated for palliation of malignant strictures in the biliary tree and argued that the regulation cited at 21 CFR 876.5010 "does not restrict these devices … to 'palliation of malignant strictures.' Nor does the regulation contain any mention of a restriction to malignant strictures," it said, adding that the agency appears to be using the guidance to modify a device classification."

The updated guidance recommends a number of new bench tests, including galvanic corrosion, stent integrity, radial compression force, radial outward force and radioparity (*IDDM*, July 23).

Cook said the test methods listed in the guidance focus on electrochemical principles that are only suited for metals and don't account for what happens to polymers that may be part of the biliary stent. It said alternative test methods, such as immersion corrosion testing should be considered suitable.

Testing

The company also took issue with requirements to test for radial outward force, stressing that a stent is a complete unit "and its radial force is dependent on the adjacent/joining sections." Therefore, "it is not possible to discretely measure the radial force of a subsection of a stent accurately as it is joined to adjacent struts/members mechanically."

Cook urged the agency to rewrite the background section because market clearance for biliary strictures is independent of vascular and other intended uses of metallic stents. It suggested adding a comment that this guidance "is not directed towards stents for vascular indications."

Boston Scientific was also critical of language in the guidance, particularly on non-clinical bench testing. It suggested the FDA remove a reference to 2006 guidelines published by S. N. Rosenbloom and R.A. Corbett on acceptance criteria for in vitro corrosion testing. The company said that the data referenced in the Rosenbloom and Corbett article presents testing performed in phosphate buffered saline, but that this test solution "is different than the simulated bile test solution recommended in this guidance, and the pitting corrosion behavior may be different between biliary stent materials tested in these two environments."

Read the Cook Medical comment here: www.fdanews.com/09-27-18-BostonScientific.pdf.

Read the Boston Scientific comment here: www.fdanews.com/09-27-18-CookGroup.pdf.

BRIEFS

Philips Monitors With Lithium Batteries At Risk

Following reports that some Philips SureSigns monitors were overheating or igniting, the UK's Medicines and Healthcare products Regulatory Agency issued a warning that lithium ion batteries manufactured by Philips that have exceeded their specified replacement interval can overheat and ignite.

Current labeling and instructions for use don't provide full instruction on when to replace the batteries, so Philips is issuing updated instructions for use and a software upgrade to provide system warnings to management on the battery replacement cycle.

Halyard Health's Ventilator Suction Cups May Interrupt Ventilation

Flex connectors in Halyard Health's closed suction kits are at risk for interrupting ventilation, the UK's MHRA warned.

The company issued an urgent field safety notice that it received reports that certain flex connectors supplied with its Halyard closed suction kits with flex connector may become loose or disconnect before or during use. If disconnection occurs during use, it would result in an open respiratory circuit and interrupt patient ventilation.

The company advised that flex connectors be replaced if there is an inadequate connection.

Scottish MPs Call for Ban On Vaginal Mesh Implants

Scotland is taking a different approach than NHS England to address concerns over vaginal mesh implants, with some members of the Scottish parliament calling for the implants to be banned for pelvic organ prolapse and stress urinary incontinence.

Scotland's Secretary for Health and Sport Jeane Freeman requested that health boards immediately halt the use of transvaginal mesh in cases of pelvic organ prolapse and stress urinary incontinence "pending the implementation of a new restricted use protocol that will ensure that procedures are carried out only under the most exceptional circumstances and subject to a robust process of approval and fully informed consent."

Scotland called on health boards to suspend the use of vaginal mesh implants in 2014. However, unless the country leaves the United Kingdom, it does not have the regulatory authority to ban the use of the mesh, as that is regulated by the UK's Medicine and Healthcare products Regulatory Agency.

FDA Warns Devicemakers Over Pen Needles

CDRH issued a Sept. 27 memo to alert device manufacturers about a post-market safety issue concerning pen needles used with pen injectors.

The hypodermic single lumen needles usually have an outer cover and a removable inner needle cover that are removed prior to injection.

In some cases, the agency said, the inside cover is not removed before injection and the intended medication is not delivered.

The FDA urged manufacturers to clearly direct patients in their instructions for use to remove both the outer and inner covers.

The agency received reports of hyperglycemia and diabetic ketoacidosis, as well as one death, associated with failure to remove the inner cover when injecting insulin.

This may be caused by patients learning to use another type of pen needle — which contains a fixed inner shield that is not removed before injection.

Currently, the FDA noted, some manufacturers provide instructions for use that may confuse consumers. While certain companies provide both written and visual graphics, others only include written instructions in their labeling, and the agency noted several cases where the instructions for use listed removal of both the outer and inner covers as one step.

Pontis Draws FDA's Attention For CAPA, Quality Violations

The FDA faulted Pontis Therapeutics for its CAPA procedures, risk analysis and quality audits following a June/July inspection of the device manufacturer's San Francisco facility.

The FDA reviewed 17 CAPA records from 2014 to 2016 and found that 12 of them had no effectiveness verification, and two CAPA records initiated in 2015 were still open. The company's chief operating officer said the firm does not verify or validate corrective or preventive actions.

The investigators also found the facility lacked product evaluations, technical reviews or studies to determine the effectiveness of one of the cycles for its Flexor Tendon Repair System.

The agency also cited the company for its risk analysis, noting that the analysis worksheet for its Flexor System includes 31 failure modes with a risk score higher than the company's risk management procedure deemed acceptable.

Investigators also found three incoming product inspection records that included materials that do not meet Pontis' QC specifications and found that nonconformance reports were generated for them.

The company failed to perform quality audits at defined intervals to determine compliance and management with executive responsibility had not reviewed the quality system's suitability and effectiveness at defined intervals, the agency found.

Read the Pontis Therapeutics Form 483 here: www.fdanews.com/09-27-18-Pontis.pdf.
— Zack Budryk

Advantages of Internal Audits

U.S., European and other regulators require devicemakers to review their operations with some degree of regularity to ensure compliance with GMP rules. Companies are free to determine exactly when, where and how these audits are carried out; still, they often look upon them as yet another burdensome regulatory requirement. But internal audits also offer a keen tool that can pare away not only noncompliant operations, but also inefficient or costly procedures.

When designing an internal audit system, as well as when actually conducting the audits, companies should look at the process in terms of the benefits it can yield. In regulatory and product quality terms, of course, an appropriately designed and implemented internal audit program can let companies identify any GMP or quality system issues before a regulator or client inspection or—even better—provide valuable information that helps to prevent issues from developing in the first place.

Wherever any corrective actions are needed, these can be put in place well before the FDA or other regulator knocks on the door, or before a client asks to review the operations of a drug or devicemaker performing contract manufacturing or providing contract laboratory services.

Then, when an inspection—regulatory or client—occurs and a particular issue is noted, the company can say that it has already identified that problem and is in the process of correcting it or, better yet, has already corrected it.

Maintaining Reputation

It's important to remember issues identified during an internal audit are confidential, whereas corrective actions are not. The confidential information includes the way in which the issue was identified and probably some of the ugliness of it under the internal audit. Some of what is uncovered during an internal audit could be things like insufficient SOPs, failure to follow critical SOPs or problems with equipment or manufacturing facilities, all things that can make a devicemaker look bad.

Corrective actions, on the other hand, should show proactive steps taken to deal with a problem or potential problem. That adds an element of robustness to your quality system. In terms of what regulators, healthcare providers, clients and the public see, the corrective actions simply show that a problem was identified quickly and addressed promptly and thoroughly, which can raise a company's profile.

Excerpted from the FDAnews management report: *Quality Management Essentials – Expert Advice on Building a Compliant System.*

Complaints, Documentation Net Richard Wolf Medical a 483

The FDA cited Richard Wolf Medical Instruments for CAPA and complaint procedures following a June 26 to July 17 inspection of the company's Vernon Hills, Illinois facility.

Agency investigators found the company's CAPA procedure did not properly identify corrective actions for non-conforming products and the facility did not adequately document corrective actions, root causes and effectiveness checks.

The facility also lacked a quality procedure or work instruction for third-party supplier corrective action requests and did not ensure that its devices were produced in accordance with federal law.

The agency also faulted the devicemaker for its complaint procedures, noting that its form for documenting complaint activities did not include a date and signature of the performer or a verifier for the investigation.

In addition, the facility failed to properly document changes to documents or equipment maintenance activities, according to the Form 483.

Read the Wolf Medical Instruments Form 483 here: www.fdanews.com/09-27-18-wolf.pdf.
— Zack Budryk

FDA Cites Meditherm Facility Over Missing Records, Procedures

The FDA flagged problems with design history files, CAPA procedures and complaint handling at Meditherm during a May inspection of the device manufacturer's Tualatin, Oregon facility.

Investigators noted that the firm had not established design control procedures and it had no design history file documenting design activities for one device, the Med2000 IRIS 7.5. The agency also found that the firm's documentation of design activities lacked a section on hardware requirements.

The facility also lacked written procedures for complaints, CAPAs or medical device reporting. For four repair records addressing complaints about its Med2000 devices, the company failed to document any reason for not investigating the complaints.

It also failed to document a review of associated data and documentation for production records for Med2000 devices manufactured since January 2017.

In addition, it lacked production records for Med2000 devices manufactured before February 2017, it had no device master record for the devices as of May 29 and it lacked procedures for quality audits, document control or products that did not conform to specified requirements.

Read the Meditherm Form 483 here: www.fdanews.com/09-27-18-Meditherm.pdf.
— Zack Budryk

FDA Seeks Feedback on Changes To Special 510(k) Program

As part of its plan to update the Special 510(k) Program, the FDA released draft guidance for stakeholder comment. The agency is considering amending the program's original rules that did not allow modifications to a device's intended use or labeling.

"We are proposing to evaluate whether design and labeling changes can be reviewed under a special 510(k) by focusing on whether the method(s) to evaluate change(s) are well-established, and whether the results can be sufficiently reviewed in a summary or risk analysis format," the draft states. Any such submissions would remain subject to all other content requirements.

To be eligible for the program, the 510(k) should be for a change to the submitter's own device, the agency said, because the program relies on previous FDA reviews of detailed information, and a device manufacturer modifying its own device is in a position to conduct the necessary risk analyses and verification activities.

In cases where devicemakers determine that they do not need to conduct further verification or validation testing to evaluate changes, they may submit the changes as a Special 510(k) application accompanied by a scientific rationale.

Applicants should include summary information based on well-established methods to evaluate the change under design controls. These should include methods, protocols and acceptance criteria used to support the previous 510(k) methods found in an FDA-recognized voluntary consensus standard, or accepted methods in the public domain, the agency said.

Read the draft guidance here: www.fdanews.com/09-27-18-510K.pdf. — Zack Budryk

APPROVALS

FDA Clears Angiography Module For Spectralis Imaging Devices

The FDA cleared Spectralis' optical coherence tomography angiography (OCTA) module for use with its new and existing diagnostic imaging devices.

OCTA is a non-invasive imaging technique that produces 3D visualization of perfused ocular vasculature.

The module allows physicians to gain better insights into ocular abnormalities.

Korea's Hironic Laser Acne Device Approved

The FDA granted approval to Hironic's AFit laser device used for treating acne.

The device, which has also earned CE Mark approval, includes a 1450 nm diode laser that penetrates into the skin's dermal and subcutaneous layers, in addition to a bipolar radiofrequency and cryogen cooling device.

The laser can treat skin conditions such as acne and acne scars, and encourage rejuvenation of the skin.

Cepheid Fingerstick HCV Test Gains CE Mark

Cepheid received the CE Mark for its fingerstick test used for quantifying viral loads of the hepatitis C virus.

The test, the Xpert HCV VL Fingerstick, detects RNA levels of the virus from blood samples and can be used in near-patient settings.

It can detect a wide range of virus genotypes in approximately one hour, so diagnosis and the start of antiviral treatment could occur within a single clinical visit.

Inui Health's Smartphone Device For Urine Testing Gains Approval

The FDA granted clearance for Inui Health's smartphone system for urine testing that covers five common tests.

Inui Health, formerly known as Scanadu, says its platform includes tests for UTIs, diabetes or pre-gestational diabetes, kidney issues and pre-eclampsia.

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

Approvals, *from Page 7*

The device allows users to instantly see their test results, rather than having to send them to a provider for analysis.

FDA Clears b-One Ortho Total Hip System

The FDA granted b-One Ortho 510(k) marketing clearance for its total hip system, used in hip replacement surgery.

The cementless device uses advanced coating technology and consists of a bone-conserving femoral prosthesis and a primary acetabular system, compatible with b-One's 12/14 taper femoral heads.

The company said the system will have a limited U.S. launch in the first half of 2019, followed by a full commercial release later in the year.

Heidelberg's Angiography Module Approved

The FDA cleared Heidelberg's optical coherence tomography angiography module, an imaging technique that gives a 3D analysis of perfused ocular vasculature.

The technology allows physicians to gain a better understanding of ocular abnormalities by using light waves to take cross-section pictures of the retina.

The device enables physicians to map and measure the thickness of the retina's layers.

FDA OK's Surgical Fluorescence For Vascular Neurosurgery

The FDA granted clearance to Leica Microsystems' Glow800 product, an augmented reality surgical fluorescence that allows surgeons to observe the cerebral anatomy in natural color.

The solution improves a surgeon's spatial orientation and the visual crispness of vessels as they perform vascular neurosurgery.

Leica Microsystems said the augmented reality fluorescence is the first of multiple imaging features it plans to release for its Glow platform.

Boston Scientific's Drug-Eluting Stent Receives FDA Approval

The FDA approved Boston Scientific's premarket approval application for its Eluvia drug-eluting vascular stent system.

The device is developed to treat peripheral artery disease by using a drug-polymer combination to continually release paclitaxel over one year.

It is designed to stop tissue from regrowing that may become an obstruction for the stented artery.

OrthoXel's Femoral Nailing System Gains FDA Clearance

The FDA granted OrthoXel 510(k) clearance for its Apex femoral nailing system, a fracture fixation device for the femur.

The system gives physicians numerous locking options, such as the patented OrthoXel micromotion for controlled axial movement, which offers torsional stability to encourage callus formation.

FDA Clears Two Oral Fluid Assays For Premier Biotech's Drug Screener

The FDA granted Premier Biotech 510(k) clearance for two additional assays used with its OralTox oral fluid drug screening device.

The Minnesota-based company's recently cleared assays are used to detect the presence of Oxycodone and Methadone in oral samples.

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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

Order your copy of **FDA and ISO Devicemaker Training Requirements** and create a training program that checks all the boxes, both in the U.S. and internationally.

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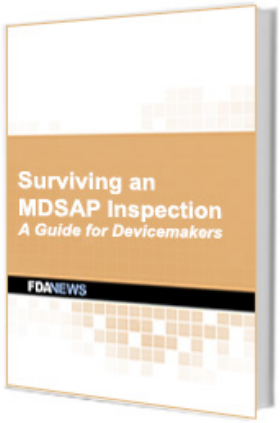

Surviving an MDSAP Inspection: *A Guide for Devicemakers*

Currently, Australia, Brazil, Canada, Japan and the United States are participating in the MDSAP program. If you pass one MDSAP inspection you'll be ready to pursue marketing authorization in five separate countries.

But, if you're going through MDSAP for the first time your experience will be very different from regulatory inspections you've gone through in the past.

- You'll know exactly when and how often to expect an audit
- You'll know exactly how long the audit will be
- You'll know exactly what questions the auditor will ask

The prescriptive nature of the MDSAP model makes it relatively easy to prepare for an audit — if you know what to expect. **Surviving an MDSAP Inspection** provides all the information you'll need to understand the MDSAP model. You'll learn:

- The standard schedule for and duration of audits
- Specific areas auditors will examine and questions they will ask
- Different types of audits involved, such as initial certification, surveillance, desk and site audits
- How to create a checklist to make sure all your bases are covered
- The MDSAP grading system and how nonconformance issues can be escalated — and consequences of getting a bad grade

The management report also includes a copy of the MDSAP Companion document — the official guide — auditors will follow.

Order your copy of **Surviving an MDSAP Inspection: *A Guide for Devicemakers*** and know what to expect from an MDSAP audit and how to prepare for it.

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