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IN THIS ISSUE

FDA Unveils Safety And Performance 510(k) Pathway

The FDA released details of its Abbreviated 510(k) review process, which it has renamed the Safety and Performance Based Pathway.

Last April, the FDA issued draft guidance proposing an expanded abbreviated 510(k) clearance program that would allow companies to show a new product's substantial equivalence to an existing device using performance criteria rather than directly comparing the device's performance to a predicate device.

Almost 20 percent of current 510(k) clearances are based on predicates that are more than a decade old, and the agency wants to promote the use of more modern predicates in order to compare devices to newer technology.

The final guidance, released on Jan. 22, focuses on the substantial equivalence analysis that requires a 510(k) submitter to demonstrate

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Shutdown That Curtailed Some FDA Inspections Ends – For Now

The FDA reopened on January 25 following a 35-day partial shutdown of the federal government that curtailed the agency's inspection activities that did not directly tie into public safety.

During the shutdown, the agency kept almost 60 percent of its workforce on hand, but suspended routine inspections. In mid-January, the agency expanded unpaid work to include surveillance and response for serious recalls, as well as inspection activities beyond "for-cause" inspections, to encompass foreign and domestic surveillance inspections for high-risk facilities and products.

"Many key functions aren't getting done. But we're focused on maintaining core activities that directly impact consumer safety and save lives," Commissioner Scott Gottlieb said.

A further shutdown is possible after February 15 when temporary funding from a continuing resolution is due to expire. — Zack Budryk

New 510(k) Pathway Could Lead to Shorter Review Times, Experts Say

The FDA's new Safety and Performance Based Pathway for 510(k) applications should be less burdensome than the longstanding Abbreviated 510(k) route to market.

The new pathway provides increased certainty regarding the likelihood of clearance for qualifying devices, said Elaine H. Tseng and Quynh Hoang, senior regulatory consultants at the law firm King & Spaulding.

The agency intends to identify the types of devices that qualify for [Safety and Performance Based Pathway] review, as well as, for each such device, the full set of performance characteristics and associated performance criteria that must be shown to achieve clearance. In some cases, the FDA may also identify the methods to be used for relevant testing. " A complete list of relevant performance characteristics, together with applicable pass criteria, should make more clear to industry the showing that will be required to ensure clearance of a device for which the SPBP pathway is available," Tseng and Hoang said.

The new pathway will also mean a shorter time to 510(k) clearance, Tseng and Hoang told *FDAnews*.

Under the current Abbreviated 510(k) pathway, for performance characteristics for which FDA has not yet specified performance criteria, applicants must show substantial equivalence through direct comparison testing against a predicate device, which is often more burdensome.

"For devices under the new SPBP pathway, FDA will publish performance criteria for all performance characteristics relevant to clearance of the device. This will enable an applicant to rely in full for 510(k) clearance on demonstrating conformity to the relevant performance criteria, " they said.

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that its device is as safe and effective as a legally marketed device. Under the program, if a predicate device meets performance criteria for safety and effectiveness and a new device meets or exceeds the same levels, the agency could deem the device as safe and effective as the predicate instead of requiring a direct comparison (*IDDM*, April 13, 2018).

The final guidance expands the concept of the Abbreviated 510(k) program by explaining how substantial equivalence for certain device types may be demonstrated in a way that is "less burdensome, but at least as robust." The approach may also make the review of 510(k) submissions more efficient, reducing burdens on the agency and possibly review times for individual submissions.

Keeping Pace With Innovation

"[O]ne of our goals is to ensure that the 510(k) program is keeping pace with the important innovations we're seeing in device development," said FDA Commissioner Scott Gottlieb and CDRH Director Jeff Shuren in a joint statement. "We believe this means that, where appropriate, new medical devices coming to market under the 510(k) pathway should either account for advances in technology that can improve the safety or performance of these products, or demonstrate that they meet more modern safety and performance criteria."

The new pathway "will modernize our approach to moderate risk devices by allowing manufacturers to use objective performance criteria established or recognized by the FDA to facilitate demonstration of substantial equivalence of their new products to legally marketed devices," Gottlieb and Shuren said.

The new pathway will ensure that the performance characteristics of new devices are evaluated against a set of objective, transparent and well-validated safety and performance metrics, the agency said.

The FDA is soliciting public comment on the guidance until April 22.

Read the final guidance here: www.fdanews.com/01-31-19-Pathway.pdf.

China Introduces Routine Overseas Device Inspections

China's National Medical Products Administration is increasing its scrutiny of foreign manufacturers and will begin routine, risk-based inspections of foreign facilities to confirm they are in compliance with Chinese regulations.

Formerly part of China's Food and Drug Administration, the NMPA began to inspect foreign device companies in 2015. As of December 2018, the agency had inspected 90 device products produced in 13 countries, according to the law firm Ropes & Gray.

The agency may also extend its inspections to R&D partners and third-party vendors.

"The Chinese regulator has shifted its regulatory philosophy from stringent pre-approval supervision to rigorous post-approval enforcement," the law firm said, and advised devicemakers intending to market or commercialize their products in China to study the statutory requirements and standards, perform internal audits, and identify and close potential gaps to mitigate enforcement risks.

FDA Issues Guidance on Therapeutic Protein Immunogenicity Tests

The FDA released guidance for sponsors of therapeutic proteins on developing tests to assess immunogenicity during clinical trials.

The recommendations apply to assays that detect one or more anti-drug antibodies (ADAs) and may also apply, on a case-by-case basis, to certain peptides, oligonucleotides and combination products, the agency said.

Sponsors should use a risk-based approach to evaluate and manage immune responses and immunologically-related adverse events for therapeutic protein products that affect their safety, efficacy, pharmacodynamics and pharmacokinetics, the agency said.

The guidance recommends several testing strategies. For example, it suggests that sponsors use a multi-tiered ADA testing approach, using a sensitive screening assay to detect small levels of low- and high-affinity ADAs. Samples that test positive in the screening assay should be put through a confirmatory assay to show ADAs are specific to the therapeutic protein product.

In some situations, sponsors should develop assays to differentiate between antibody isotypes. For example, results from antigen-specific IgE assays may be informative for therapeutic protein products with a high risk of anaphylaxis or for which anaphylaxis has been observed, the agency said.

"Immunogenicity tests should be designed to detect ADA that could mediate unwanted biological or physiological consequences such as neutralizing activity or hypersensitivity responses," the agency said.

Read the full guidance here: www.fdanews.com/01-23-19-ImmunogenicityTesting.pdf.
— James Miessler

HSCC Introduces Plan For Cybersecurity 'By Design'

The Healthcare and Public Health Sector Coordinating Council (HSCC) has developed a new guide for managing the security of medical devices.

The Medical Device and IT Joint Security Plan (JSP) is a total product lifecycle reference guide that uses "security by design" principles for devices and health IT solutions.

Aimed at improving information sharing between devicemakers and healthcare organizations, the plan stresses joint responsibility among industry stakeholders to harmonize security standards, risk assessment methodology and reporting vulnerabilities.

Roughly 200 device companies and health IT companies, healthcare providers and payers provided feedback on the plan. The JSP task force

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HHS Inspector General: Smartphone App Won't Violate Kickback Laws

The Health and Human Services inspector general has green-lighted a sponsor's request to offer smart phones to poor patients so they can take an antipsychotic drug with an electric sensor.

The sponsor's name was redacted from the IG's document but a spokesman for Otsuka America Pharmaceuticals confirmed to *IDDM* that it stemmed from his company's request to hand out smart phones to patients taking Otsuka's Abilify MyCite, a drug-and-device combination antipsychotic.

Otsuka told the IG it wanted to use a smart phone app to help ensure that patients took Abilify on time and correctly. The drug has an electronic signal that records when it has been taken, which would eventually be recorded on a smartphone app.

But some unidentified numbers of patients who need the drug can't afford a smartphone and Otsuka was concerned that loaning out phones with the app would violate rules against inducements and anti-kickback laws.

In a letter released last week, the IG said that, even if the smartphone could "potentially" violate the anti-kickbacks law, HHS won't pursue any charges as long as Otsuka agrees to strip the phone down so that it's mostly focused on registering doses.

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was co-chaired by representatives of Becton Dickinson, the Mayo Clinic and the FDA.

Although not a standard, device companies can voluntarily commit to the joint security plan and healthcare providers can request its use by vendors.

"Securing medical devices from cybersecurity threats cannot be achieved by the FDA on its own," said Suzanne Schwartz, CDRH's associate director for science and strategic partnerships. "That's why the FDA has long been committed to working hard with various stakeholders like the HSCC to stay a step ahead of constantly evolving cybersecurity vulnerabilities."

The JSP was formed in response to recommendations issued in June 2017 by the Health Care Industry Cybersecurity Task Force, which called for stronger efforts to increase the security and resilience of medical devices and health IT. The HCIC was established by HHS under the Cyber Security Act of 2015.

The plan will help hospitals to minimize cyber vulnerability and help device manufacturers reduce the cost and complexity of mitigating device risks. The plan covers four key themes:

- Design control – building medical technology with cybersecurity standards and testing;
- Complaint handling – preparing and managing deployed medical technology cybersecurity;
- Risk management – assessing and responding to cybersecurity issues and events throughout the medical device lifecycle; and
- Maturity evaluation – measuring and tracking progress of a cybersecurity program for devices.

In October 2018, the FDA guidance for sponsors of devices with cybersecurity risks on what they should include in their premarket submissions, as well as considerations for device design and labelling (*IDDM*, Oct. 19, 2018).

The Office of Inspector General issued a recent report in the fall that said the FDA needs to do more to reduce postmarket cybersecurity risks (*IDDM*, Nov. 2, 2018).

Roughly 95 percent of healthcare institutions said they were targeted for some form of cyberattack, the report said, noting that about 80 percent of device manufacturers have less than 50 employees and said they need guidelines and help with security.

Read the JSP here: www.fdanews.com/02-01-19-JSP.pdf.

Ecleris Scolded For Procedural Issues

EUSA Global, doing business as Ecleris USA, drew a Form 483 after an FDA inspection revealed problems with CAPA procedures and management reviews, among other issues.

During its Oct. 11-17, 2018 inspection of the firm's Medley, Florida site, the agency found deficiencies with one of the two CAPA records available for investigation. The record involved engineering changes put in place by the corporate headquarters for a medical fiberoptic light source that were not announced to the facility.

While the root cause was identified as an inadequate process to transfer design changes from HQ to the facility, the plan didn't sufficiently address the root cause. The record also lacked approval signatures needed for initiation and had no documentation of completed corrective actions or the status of unfinished ones. No documentation was included for the effectiveness verification criteria, and no follow-up on the CAPA was given.

The firm also didn't have complaint files ready for review during the inspection — for microscopes, light sources, colposcopes, sinuscopes and surgical headlights the firm either manufactured, assembled, repackaged or relabeled.

In addition, the firm didn't document all personnel training. For example, one auditor who participated in the five internal audits of the firm's quality system in 2018 was missing qualifying documentation. In another instance, the training record for the firm's warehouse associate — who was seen conducting packaging and shipping activities during the inspection — was missing training documentation for the firm's shipping procedure.

Read the Ecleris USA Form 483 here: www.fdanews.com/01-31-19-eusa483.pdf. — James Miessler

CAPA Investigation Strategy Meetings

Each CAPA investigation should start with a strategy meeting. The lead investigator, who is typically the head of quality assurance, must determine whether the meeting should be formal or informal and what it should accomplish. The lead investigator also must decide who should participate. To maximize an investigation's effectiveness, the company should gather everyone who understands the situation, including both high-level experts and frontline staff. Participants might include individuals from engineering, R&D, laboratory, production or QA. Certainly, the type of incident or deviation will help dictate attendance.

The meeting should serve as a way to gather information and should address both issues of fact (what is known) and suspicion (potential root causes), yet take care to separate fact from opinion. During the meeting, team members must determine what additional information they require and from whom to get it; prepare to communicate with the appropriate stakeholders; and clearly define the next steps of the investigation. The company should fully analyze the situation before moving on and examining what factors contributed to the problem.

The individual team members should resist the tendency to work on their own in a "silo." Unfortunately, such a tendency arises when people grow defensive about their functional areas. An adequate investigation calls for teamwork, with input and information from all affected areas. The primary method for conducting investigations is called root cause analysis.

Root cause analysis (RCA) is a step-by-step method of investigation that should lead to the underlying cause of an incident or nonconformity that triggered a CAPA investigation. RCA provides feedback on a company's operational performance.

RCA helps answer these fundamental questions:

- What went wrong?
- What were the consequences of the incident(s)?
- What could cause these events?
- What changes should be made to the proactive analysis process and the management systems to adequately control risk in the future?

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

Inadequate Document Control Lands Stand Aid in Hot Water

The FDA flagged Stand Aid of Iowa in a Form 483 over shoddy document control, device history records and documentation of nonconforming product activities seen at its Sheldon, Iowa facility during an Oct. 22-23, 2018 inspection.

The devicemaker was cited for failing to document nonconforming product activities, including investigation, evaluation, reworking, scrapping and part returns.

Some of the firm's device history records for its Econo-Stand 1600 device didn't document that the devices were manufactured with the correct parts or correct number of parts, which are specified in the product's manual bill of materials.

Additionally, certain quality system documents were not signed by a designated individual and didn't contain dates of approval, including a device history record procedure, a rework procedure, an acceptance activities procedure and a document change and control form.

Read the Stand Aid of Iowa Form 483 here: www.fdanews.com/01-31-19-standaidofiowainc483.pdf. — James Miessler

Imaging Biometrics Cited For Complaint Investigation Records

The FDA hit Imaging Biometrics with a Form 483, calling the Elm Grove, Wisconsin healthcare software developer out for its medical device reporting procedure and complaint records.

The agency, which inspected the facility from Oct. 3 to 12, 2018, found that multiple closed complaint records at the facility lacked investigation details. The summary information recorded in the complaint records of five out of six closed complaint records did not line up with the information reported by the complainant.

Furthermore, six complaint records did not include enough information to support the firm's decision not to file them as medical device reports. For example, two complaints reported a problem, but the firm had no objective evidence to support follow up with the complainants to gain additional information that could verify the firm's decision not to report the incidents.

The firm's written MDR procedure for customer complaints did not have a standardized review process that defined terms used to determine if an event meets the criteria for reporting a MDR, or who would decide if a MDR is reported. The procedure also gave no examples of what the firm viewed as reportable events.

Read the Imaging Biometrics Form 483 here: www.fdanews.com/01-31-19-imagingbiometricsllc483.pdf. — James Miessler

BRIEFS

J&J, DePuy Settle State Hip Implant Cases for $120 Million

Johnson and Johnson and its DePuy subsidiary agreed to pay $120 million to settle multistate lawsuits alleging false claims and unfair marketing of their metal-on-metal hip implant devices.

The 46 states that accused DePuy of making false claims about the longevity of the ASR XL and Pinnacle Ultamet metal-on-metal hip implant devices will share the settlement. Texas, for example, will receive $8.5 million.

Under the agreement, DePuy will reevaluate and revise its marketing and promotion strategies for the hip implants, including its use of scientific data to support advertising claims. The company said the settlement involves no admission of liability or misconduct.

Researchers Develop New Blood Flow Imaging Tool

A research team at Northwestern University has developed a 3-D imaging device that can track blood flow through capillaries.

The device can detect tiny changes in capillaries using spectral contrast optical coherence tomography angiography (SC-OCTA) — a 3D-imaging technique useful for early identification of diseases.

The technology doesn't depend on injected dyes for contrast and requires no radiation. It can also image blood whether it's stagnant or in motion, allowing it to image the heart and other moving organs.

"There has been a progressive push to image smaller and smaller blood vessels and provide more comprehensive, functional information," says Vadim Backman, the team's leader. "Now we can see even the smallest capillaries and measure blood flow, oxygenation and metabolic rate."

The device currently cannot image deeper than one millimeter, but that can be circumvented by attaching the tool to an endoscopic probe, which enables it to perform close-up imaging of a patient's organs.

French Regulators Greenlight Ultrasound Trial for Glioblastoma

French regulators approved a Phase I-2 clinical trial of an ultrasound device to treat recurrent glioblastoma.

French-based CarThera is hopeful that its implantable SonoCloud-9 will help open up the blood-brain barrier in patients with recurrent glioblastoma who are eligible for carboplatin chemotherapy.

The device issues low-intensity pulsed ultrasound and it's already proved safe and effective for patients in the short-term. The company has just won French approval for an open-label dose escalation study that will enroll 20 patients over the next year.

CarThera officials are hoping for FDA approval to extend the trials to the U.S., in the MD Anderson Cancer Center in Houston and Northwestern Memorial Hospital in Chicago.

APPROVALS

FDA Clears Verily's ECG Device

Alphabet subsidiary Verily's Study Watch received 510(k) clearance for its electrocardiogram feature, allowing the device to record a patient's ECG rhythms.

The wearable device can store, transfer and display single-channel ECG rhythms and is indicated for use by healthcare professionals, health conscious patients and adults with heart conditions.

The device enables the scalable collection of data in clinical and observational studies. It has previously been used in clinical trials to capture participants' health information.

Biom'up's Laparoscopic Applicator Earns New Marketing Approval

The FDA granted Biom'up's Hemoblast Bellows laparoscopic applicator marketing approval for all minimally-invasive procedures.

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

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The approval expands the device's indications and allows surgeons to use the hemostatic powder in both traditional and laparoscopic surgeries.

The device is used to quickly deliver Hemoblast powder to bleeding areas in minimally-invasive surgeries, providing control of minimal, mild and moderate blood flows.

FDA Clears RFPi's Blood Flow Imaging Device

The FDA granted 510(k) clearance for RFPi's iCertainty, a non-invasive blood flow and perfusion imaging device for use in surgical procedures.

The device shows a patient's blood flow without interrupting surgery or requiring dyes, radiation, injections or direct patient contact.

The product is cleared for imaging blood flow and perfusion in tissue up to 4-5mm in depth. It's initial uses include lower-leg vascular procedures and gastrointestinal and plastic surgeries.

Tivic Health's Sinus Pain Reliever Device Cleared

Tivic Health received 510(k) clearance for its ClearUP bioelectronic sinus pain reliever, a device that relieves pain from hay fever.

The non-invasive device targets the most effective areas on the patient's skin and uses microcurrent waveforms to provide pain relief.

ClearUP's design allows it to slide across the outside of the nasal passages as it applies low current electrical waveforms to stimulate nerves and relieve pain.

Gramercy's Nitinol Staple System Cleared by FDA

Gramercy Extremity Orthopedics received FDA clearance for its Nitinol staple system for treating bone-related conditions.

The staple system is cleared to fixate osteotomies and small bone fragments. It's also cleared for joint fusion surgery.

The device provides an array of sterile symmetric and asymmetric, barbed and smooth nitinol staples that come in various widths and lengths.

IschemaView Gains Expanded Clearance for Neuroimager

The FDA handed medical imaging developer IschemaView expanded clearance for its Rapid neuroimaging platform.

The imaging platform is intended for use in selecting stroke patients that are expected to benefit from endovascular thrombectomy, which treats strokes by pulling blood clots out of arteries.

The company said the Rapid system is the only imaging platform currently approved for selecting stroke patients for blood clot removal.

FDA Clears Immuno Concepts' Rodent Tissue Slides

The FDA granted 510(k) clearance for Immuno Concepts' Histofluor rodent liver, kidney and spleen tissue slides.

The rodent tissue slides are available in both mouse and rat substrates, and all components come ready-to-use.

The slides can be used manually or with Immuno Concepts' Image Navigator device, an automated microscope that can capture multiple images and assemble them into a panoramic view.

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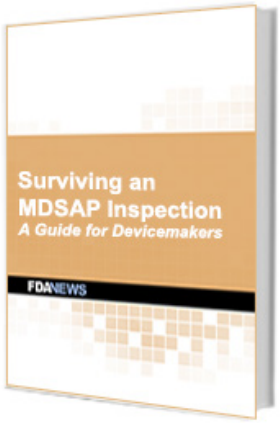

Surviving an MDSAP Inspection: *A Guide for Devicemakers*

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.

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

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Complaint Management for Devicemakers: *From Receiving and Investigating to Analyzing Trends*

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Understanding the FDA's Quality System Regulation isn't enough — you must also master ISO 13485:2016 and the new EU MDR. They all require devicemakers to conduct trending in some form or another. But none of them tell you HOW.

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