INTERNATIONAL DEVICES & DIAGNOSTICS MONITOR

Vol. 4, No. 31
Aug. 6, 2018

IN THIS ISSUE

FDA Releases Guidelines For 'Small' Businesses on MDUFA Fees

The FDA issued guidance for small businesses seeking a discount on medical device application user fees or a waiver for a first premarket application fee and began accepting small business certification requests for fiscal 2019 on Aug. 1.

The agency is raising its standard fee for pre-market applications, product development protocols or biologics license applications to $322,147, up from $310,764 for fiscal 2018. But qualified small businesses will pay much less for the applications, as well as premarket reports and efficacy supplements: $80,537 for each. Small-business 510(k) premarket notification submissions will cost $2,738 and de novo classification requests will cost $24,161.

The fiscal year 2019 user fees, which devicemakers pay when they register their establishments and list their devices with the

(See **Business**, *Page 2)*

IMDRF Opens Consultations on AERs, Principles for Labeling and UDIs

IMDRF's Adverse Event Terminology Working Group is seeking comments on proposals to harmonize terminology globally for reporting adverse events for medical devices and in vitro diagnostics.

The use of a single adverse event terminology and coding system is expected to improve signal detection by adverse event management systems to allow faster responses by both industry and regulators. Using defined terms and associated codes will help identify potential risks sooner and allow sophisticated trending analyses among global regulators.

The working group released updated IMDRF terminologies for categorized AERs in September 2017. The new consultation covers additional annexes on health effects terms and conditions based on FDA terms and it refers to MedDRA. An annex on components is still under development.

(See **IMDRF**, *Page 6)*

Insys Buprenorphine Spray Draws Complete Response Letter

The FDA issued Insys a complete response letter citing safety concerns over the company's NDA for a buprenorphine sublingual spray indicated for moderate-to-severe acute pain.

The CRL followed an FDA advisory committee meeting in May that found the company demonstrated statistically significant efficacy data but noted concerns about the safety data.

The company said it continues to believe that the drug-device combination "could bring value to the management of pain and will assess the next steps in the context of the company's overall mission."

Business, *from Page 1*

agency, whenever they submit an application or a notification to market a new medical device in the U.S., and for certain other types of submissions for, go into effect on Oct. 1.

To qualify for the lower fees, a business must have gross receipts or sales of no more than $100 million for the most recent tax year. That includes the gross receipts of any affiliates, including parent companies or subsidiaries.

Business can qualify for a "first premarket application/report" fee waiver if they (and their affiliates) have gross receipts or sales of $30 million or less, so long as the FDA determines that the neither the organization nor its affiliates have previously submitted a premarket application/report—whether or not it was approved.

Organizations that have applied in the past will find the process "substantially similar" to the FY 2018 guidance. But the FDA says it "continues to make quality improvements in the program, in areas such as administrative completeness and consistency of documentation," in order to help applicants develop and submit their certification requests and for the FDA to review the requests in "a consistent, timely manner."

The FDA says it will review application forms and supporting materials within 60 days, then will notify businesses whether or not they qualify. Status as a small business begins on the date of FDA's decision letter and expires at the end of the fiscal year. Companies must submit new requests and supporting documents annually.

If a business submits an application before going through the small-business certification process, it will have to pay the standard fees; there are no refunds. Businesses that hope to qualify as small businesses should not submit an application that requires a fee until they have a ruling from the FDA and a small business decision number.

The final day to submit an application is Sept. 30, 2019.

The guidance also includes instructions for foreign businesses and U.S. businesses with foreign affiliates as well as step-by-step directions for filling out the relevant FDA forms.

Read the full guidance here: www.fdanews.com/08-02-18-UserFee.pdf. — Gienna Shaw

Menstrual Cup Maker Anigan Warned for Serious GMP Violations

The FDA handed a warning letter to Anigan for numerous GMP violations it uncovered during an April 2018 inspection of the firm's San Ramon, California facility.

The agency issued the devicemaker a Form 483 on April 19 at the close of the inspection for failure to establish design control procedures, validation procedures, risk analysis, or complaint handling procedures for its Class II Super Jennie and EvaCup reusable menstrual cups.

The company provided a design control procedure during the inspection, but it didn't have an implementation date or evidence that it had been reviewed or approved.

"You told our investigator it became effective on April 6, 2018, and that prior to that date your firm had not established design controls for your menstrual cups since 2014," the agency said.

In its response to the 483, Anigan said it hired a consultant and would have a plan in place by June 30 for retroactively completing the design controls. However, the FDA said the devicemaker hadn't provided any objective evidence of corrections and it hadn't addressed how it would ensure products distributed would conform to user needs.

At the time of the inspection, the firm had no evidence that it had validated designs for either the EvaCup or the Super Jennie cup. The firm provided instructions for use that recommended cleaning the cups in boiling water to initially sterilize them, but it had not conducted validation studies or risk analyses for either of the devices.

No Validation or Risk Analysis

The firm's website said the cups could be used for up to 12 hours, but no validation tests or risk analysis was conducted to simulate use conditions, the agency said.

In its response, Anigan said it removed a reference for soaking the cups in peroxide solution, but it didn't provide evidence to support this correction, and there was no discussion about labeling. The firm said it planned to initiate biological testing and sterilization validation with an "acceptable testing lab" by July 1, but no additional details were provided, and the FDA said it couldn't evaluate the adequacy of the response.

The firm had not considered other potential risks such as the inability of the user to remove the device, placing the device incorrectly, use with an IUD, use after the birth of a baby, use of colored silicone inside the vagina, or compatibility of the silicone with the recommended lubricant for inserting the device.

Complaint Handling

The FDA said it was unsatisfied with Anigan's response that it would develop a risk analysis procedure by June 30 and have a risk analysis plan in place by July 15, because the company did not include adequate details.

Although Anigan had received roughly 60 complaints about the menstrual cups, it did not have procedures in place for receiving, reviewing and evaluating complaints. At the time of the inspection, no complaints records were provided to the investigator. As with the other citations, the FDA said it could not determine the adequacy of the firm's response because it hadn't provided objective evidence of corrections.

The FDA took issue with Anigan for its inability to determine if the devices meet specifications, noting it did not establish specifications for all of its packaging and labeling, and it had no device acceptance records for any of the menstrual cups.

Procedures for quality audits had not been established nor had the firm conducted management reviews, the agency said.

"Your firm's Audit Log is blank and no records of audits were provided to show a single internal audit had been performed since you began manufacturing and distributing menstrual cups in 2014," the letter said.

Read the warning letter here: www.fdanews.com/08-02-18-Anigan.pdf.

MedTech Europe Raises New Concerns Over MDR/IVDR Timelines

MedTech Europe sounded a new alarm about the limited time available to implement the EU's new medical device regulations and in vitro diagnostic regulations that go online May 2020 and May 2022 respectively.

The association is calling on regulators to either extend the critical dates to May 2022 for all products, or to stop the clock and freeze the remaining transition time until the system is ready.

Although devicemakers are investing heavily to comply with the new regulations and will be ready to submit files to maintain the supply of devices to the market, regulators have been slow in implementing needed infrastructure to enable the regulatory system to work, the association said.

"The industry is calling urgently on the European Commission, the European Parliament and all EU Member States to provide solutions that will rapidly install the functionality of the new regulatory systems and thereby safeguard the continued availability of life-saving and life-transforming medical technology products," MedTech Europe said.

Failure to take action now could seriously jeopardize devicemakers' ability to keep products on the market, the association warned.

Progress has been slow in putting in place the needed elements of the regulatory system, including:

- Notified bodies that need to be re-designated before they can assess or re-certify compliance for devices and IVDs with the new regulations;
- Implementing Acts — only two out of 18 system-critical implementing Acts have been published;
- Expert panels, reference laboratories and common specifications are essential for certain new products and high-risk devices to be CE marked;
- Standards and guidelines are needed for industry to provide a common interpretation on how to apply the regulations; and
- The Eudamed database needs to be ready on time to strengthen market surveillance and transparency.

The association stressed that there are limited resources available for notified bodies to recruit and train personnel to address the requirements of the new regulations. And, with more requirements under the new regulations, industry is concerned that notified bodies will not be able to handle the workload.

In addition, it remains unclear how Brexit will affect the transition process, particularly when roughly 30 percent to 40 percent of devices in the EU are certified through UK notified bodies. It is not clear whether the notified bodies will continue to operate in the EU or if the certificates for these products will continue to be valid in the EU.

Grace Period Is No Solution

Regulators have stressed that a grace period ending on May 26, 2024 would allow for certain devices to be placed on the market with a valid certificate beyond the end of the transition periods. However, the grace period doesn't provide a system-wide solution because certificates based on the current directives must still be renewed before May 26, 2020 for devices and before May 26, 2022 for IVDs, the association said.

This creates an enormous increase in demand for renewals of certificates, and notified bodies must manage these renewals at the same time they are handling new obligations under the new regulations. In addition, there is no grace period option for products that don't require a notified body certificate under current regs but will require it under the new regs.

The association said the grace period could be more effective if it was extended to include all products and was more flexible.

One year after the introduction of the new regulations, there remains a mountain of work to

(See **MedTech***, Page 6)*

IMDRF, *from Page 1*

The adverse event reporting terminology is composed of four sets of terminologies:

- Medical device problem terminology;
- Components terminology;
- Cause investigation terminology; and
- Health effects terminology.

The guidance covers what adverse events should be reported, to whom they should be reported and when they should be reported as well as how to report them.

The move aligns with the FDA's plans to update its adverse event codes and to deploy CDRH's electronic medical device reporting system and eSubmitter software. To reduce ambiguities, each term is uniquely identified by an alphanumeric code and is explained by a definition and examples.

Code hierarchies posted on FDA.gov are linked to IMDRF codes as the agency ultimately plans to harmonize all adverse event codes with IMDRF terminologies (*IDDM*, April 27).

The comment period on the proposed guidance closes Oct. 12.

Labeling Principles

IMDRF's Good Regulatory Review Practices Working Group released a new document on the Principles of Labeling for Medical Devices and IVDs. The guidance covers label content and instructions for use to support the safe use of devices and IVDs. It includes references, standards, definitions and principles for identifying devices and IVDs.

The guidance was developed to support global convergence of regulatory systems and is to be used by regulators, conformity assessment bodies, industry and others. It covers general labeling principles for devices and IVDs, including labeling for single-use devices, software as a medical device, and devices and IVDs intended for use by lay persons.

The guidance notes that a device or IVD should be identifiable via a method that allows differentiation from other products of the same type, and it should be identified with a catalogue number. A unique device identifier may also be required, which should be linked to a catalogue number in the UDI database. UDIs need to be issued by an accredited issuing agency/entity that conforms to international standards.

The comment period closes on Sept. 12.

UDI Application Guide

The IMDRF UDI Working Group released a UDI System Application Guide for use as a supplement to the UDI guidance. The application guide is intended to assist stakeholders within the supply chain to understand the role and impact of the UDI system.

The guide includes references and definitions of the UDI system as well as the fundamental elements of a globally harmonized UDI system and guiding principles for UDI system design and operations.

The UDI system is being formed across different jurisdictions across the healthcare sector, and when fully implemented, the labels of most devices will include a UDI in human- and machine-readable form.

The comment period closes on Oct. 12.

Read the three IMDRF consultation documents here: www.fdanews.com/07-31-18-IMDRF.pdf.

MedTech, *from Page 5*

be done, said Oliver Bisazza, MedTech Europe's regulations and industrial policy director. Aside from the new Eudamed database, nearly 16 other implementing acts are needed, he said.

"Industry is growing more nervous every day, as it seems increasingly likely that we will have too few notified bodies, available too late, covering too few product categories, and (above all) with far too little capacity," Bisazza said. "The vast majority of IVDs and medical devices cannot be transitioned to the new rules without a notified body" (*IDDM*, June 8).

Siemens Healthcare Diagnostics Flagged for CAPA Issues

Siemens Healthcare Diagnostics fell short on CAPA procedures, acceptance activities and equipment maintenance, the FDA said in a Form 483 issued the form after a February/March inspection of the devicemaker's East Walpole, Massachusetts, facility.

FDA officials found the company failed to verify the effectiveness of three CAPAs and its investigations of deviations or out-of-specification results observed during quality control acceptance activities were not properly documented, the agency said.

The FDA also faulted the Siemens facility for not properly verifying the accuracy of the reagent expiration dates its software calculated and generated.

Lastly, according to the FDA, the company produced no documentation for preventive equipment maintenance activities performed in its controlled temperature rooms, including coolers and freezers used for storage, handling and processing of products.

Read the Siemens Healthcare Diagnostics Form 483 here: www.fdanews.com/08-02-18-siemenshealthcarediagnosticsinc483.pdf. — Zack Budryk

FDA Raps OptumHealth Over Quality Audits, Complaints

The FDA found design verification and quality audit deviations in a February/March inspection OptumHealth Care Solutions facility in Rye Brook, New York.

Investigators found the firm had no procedure in place requiring the company to review the results of its contract firm's verification activities. The contract firm also had no documentation demonstrating it had reviewed the design verification it provided.

The firm's procedures for design revisions also did not define what is considered a "major" or "minor" change, according to the 483, relying instead on a contract firm's definition, which the agency deemed inadequate. Investigators also found the design input for the Optum TeleHealth Application software did not include proper documentation of reviews and approval for changes.

The firm's complaint-handling procedures did not accurately specify responsibility for certain complaint-handling and complaint determination functions, and did not state job titles. Similarly, its quality audit procedure did not specify the frequency of audits.

Lastly, OptumHealth failed to properly define certain job titles or individuals for certain functions within the company's management review procedure, the agency said.

Read the full 483 here: www.fdanews.com/08-02-18-optumhealthcaresolutionsinc483.pdf. — Zack Budryk

APPROVALS

Roche Gains CE Mark For Insulin Micropump Device

Roche received a CE Mark for its Accu-Chek Solo insulin micropump system, offering tube-free delivery and personalization.

The system is made up of two parts – a semi-disposable, lightweight insulin micropump and a remote control that includes blood glucose monitoring and dosage advice.

Users can administer dosages directly from the pump or with the handheld remote and the pump can be taken off and attached without wasting insulin.

MedicalGorithmics' Mobile Cardiac Rehabilitation System Cleared

The FDA granted 510(k) clearance for MedicalGorithmics and U.S. subsidiary Medi-Lynx Cardiac Monitoring's PocketECG cardiac rehabilitation system.

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

Approvals, *from Page 7*

The device is used during rehabilitation training for automated arrhythmia detection and electrocardiography (ECG) monitoring.

The device, about the size of a smartphone, monitors the heart rate and heart rhythm of patients during rehabilitation exercises to automatically detect abnormalities and arrhythmias, helping them stay aware of workout safety and intensity.

Israeli Devicemaker Cleared For Urinalysis Test

The FDA granted Healthy.io 510(k) clearance for its home-based urinalysis test Dip.io device that enables a smartphone to read urine tests.

Dip.io comes with testing cups, disposable test strips and instructions for home testing. In addition, a panel of colors and patterns allows the smartphone to read the test strip regardless of lighting.

The test kit gives immediate results for clinical-grade urine tests and does not require mailing.

Co-Diagnostics' IVD For Tuberculosis Gets CE Mark

Co-Diagnostics received a CE Mark for its Logix Smart MTB test, an in vitro diagnostic for diagnosing tuberculosis.

Tuberculosis was listed by the World Health Organization as one of the top ten causes of death globally. The disease often shows no early symptoms, leading to late diagnosis that can prove fatal.

The company is not currently seeking FDA approval for the IVD, as the U.S. has a low domestic rate of tuberculosis incidents.

PerkinElmer Receives Clearance for Two Assays

The FDA granted 510(k) clearance for two new PerkinElmer assays developed by its Euroimmun subsidiary.

The assays screen and diagnose anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis, disorders that can be hard to diagnose.

The two assays provide reliable ANCA screening results and eliminate the need to run several analyses for each sample.

Reva's Bioresorbable Scaffold Earns CE Mark

Reva announced that its Motiv bioresorbable scaffold received a CE Mark for treating below-the-knee peripheral artery disease.

The device is made from a proprietary polymer designed specifically for use in vascular scaffolds.

The scaffold is used for patients experiencing critical limb ischemia, a severe artery blockage of the lower extremities, and is visible under x-ray for accurate placement in the

Adherium Gains Clearance For OTC Sales of Hailie Sensor

The FDA granted additional 510(k) clearance for the Adherium digital health platform, clearing over-the-counter sales of its Hailie sensor, a device designed for use with asthma inhalers.

The sensor, previously known as Smartinhaler, attaches to a patient's asthma or COPD inhaler to monitor and encourage consistent use, allowing patients to self-manage their asthma treatment.

FDANEWS

Customer Service
(888) 838-5578 • +1 (703) 538-7600
customerservice@fdanews.com

Editorial: Declan Conroy
+1 (703) 538-7644
dconroy@fdanews.com

Ad Sales: Jim Desborough
+1 (703) 538-7647
jdesborough@fdanews.com

Multi-User Sales: Jeff Grizzel
+1 (703) 538-7669
jgrizzel@fdanews.com

300 N. Washington St., Suite 200 • Falls Church, VA 22046-3431 • Phone: (888) 838-5578 • +1 (703) 538-7600 • www.fdanews.com

Reporters: Zack Budryk, James Miessler, Bill Myers

President: Cynthia Carter

FDANEWS

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.

FOUR EASY WAYS TO ORDER

1. **PHONE:** Toll free (888) 838-5578 or +1 (703) 538-7600
2. **WEB:** www.fdanews.com/55623
3. **FAX:** +1 (703) 538-7676
4. **MAIL:** FDAnews 300 N. Washington St., Suite 200 Falls Church, VA 22046-3431

☑**Yes!** Please send me ____ copy(ies) of ***EU MDR Compliance: A Checklist for Meeting Manufacturing, Safety and Performance Requirements*** at the price of $397 for each PDF.

Name _____

Title _____

Company _____

Address _____

City_____ State _____ Zip code _____

Country _____

Telephone _____

Fax _____

Email _____

METHOD OF PAYMENT

❑ Check enclosed (payable to FDAnews)

❑ Bill me/my company. Our P.O.# _____

❑ Charge my credit card:
❑ Visa ❑ MasterCard ❑ American Express

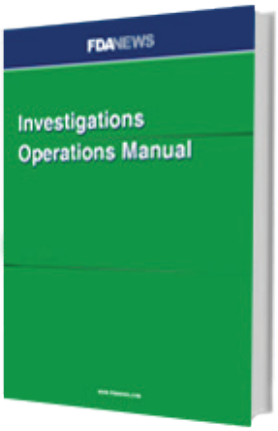
Credit card no. _____

Expiration date _____

Signature _____
(Signature required on credit card and bill-me orders)

Virginia customers add 6% sales tax.

18FLYR-N



Investigations Operations Manual 2018

The **Investigations Operations Manual** is the primary policy guide for FDA investigations and directs the conduct of all fundamental field investigational activities. Adherence to the manual is required.

Now you can have the same investigation manual for 2018 that the FDA investigators use.

Know what the investigators look for — before they even get there. Know the investigators' expectations and rights. Find and fix problems *before* they end up on a Form 483 or warning letter.

There is no better way to prepare for an inspection than studying the actual procedures the FDA teaches its investigators.

Available directly from FDAnews, the newly updated edition of the **Investigations Operations Manual 2018** is the primary source FDA investigators use to conduct field inspections.

Order today.

Get insider information on:

- Sampling techniques
- Import hold procedures
- Recalls
- Types of investigations
- And more…

Make sure you've got the *latest* version before the FDA knocks on your door.

FOUR EASY WAYS TO ORDER

1. **PHONE:** Toll free (888) 838-5578
   or +1 (703) 538-7600
2. **WEB:** www.fdanews.com/55983
3. **FAX:** +1 (703) 538-7676
4. **MAIL:** FDAnews
   300 N. Washington St., Suite 200
   Falls Church, VA 22046-3431

☑**Yes!** Please send me ____ copy(ies) of **Investigations Operations Manual 2018** at the price of $377 for each PDF.

Name _____

Title _____

Company _____

Address _____

City_____ State _____ Zip code _____

Country _____

Telephone _____

Fax _____

Email _____

METHOD OF PAYMENT

❑ Check enclosed (payable to FDAnews)

❑ Bill me/my company. Our P.O.# _____

❑ Charge my credit card:
❑ Visa ❑ MasterCard ❑ American Express

Credit card no. _____

Expiration date _____

Signature _____
(Signature required on credit card and bill-me orders)

Virginia customers add 6% sales tax.

18FLYR-N