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IN THIS ISSUE

Devicemakers See Lower Fees Under MDUFA 2017

Devicemakers will pay almost $27,000 less for premarket applications for medical device user fees in fiscal year 2017.

The new fees go into effect Oct. 1 through Sept. 30, 2017. Companies will need to pay the correct fee when they submit applications or they risk having their applications rejected, the agency said in its July 28 notice. The statute authorizes the FDA to collect $140.762 million in user fees.

Similar to the fee structures announced for PDUFA, GDUFA and BsUFA, the FDA's MDUFA fees are slightly lower across the board for FY 2017 compared to FY 2016.

For example, the standard fee for a premarket application is $234,495 for FY 2017 compared to $261,388 in FY 2016. The annual registration fee for FY 2017 is set at $3,382 compared to $3,845 in FY 2016.

(See **MDUFA***, Page 2)*

EU Medical Device Regulations Are Coming – Is Your Company Ready?

The European Commission is drafting the final medical device regulations, and regulatory affairs professionals should already be conducting gap analyses to understand the impact of the regulations on their companies.

The changes will have far-reaching implications across multiple business units, including product development, clinical, regulatory affairs, manufacturing and supply chain operations.

The regulation will add complexity for high-risk devices, particularly when it comes to submissions, said Judith Meritz, strategic advisor at YourEncore, during a recent FDAnews webinar. Also, more products will be classified under the regulation that were not previously classified as medical devices (*IDDM*, May 27).

(See **EU MDR***, Page 4)*

FDA Won't Regulate Low-Risk Wellness Devices

The FDA has determined that low-risk general wellness devices that promote a healthy lifestyle will be exempt from regulation.

CDRH defines wellness devices as products that are intended for only general wellness use, as defined in final guidance released July 28.

The final guidance remains little changed from draft guidance released on Jan. 20, 2015. The biggest change is in section six of the guidance, which presents a decision algorithm for determining whether general wellness products are within the scope of the guidance.

The guidance clarifies that general wellness products fall into two categories: those that are intended to encourage a state of health or healthy activity, or to help reduce or impact certain chronic diseases "where it is well understood and accepted that healthy lifestyle choices may play an important role in health outcomes for the disease or condition," the guidance says.

(See **Low-Risk**, *Page 6)*

MDUFA, *from Page 1*

There is no small business rate this year, the FDA said; however the small business rate is 25 percent of the standard full fee.

Companies wanting to qualify as a small business must have gross sales less than $100 million for the most recent tax year. Businesses with sales less than $30 million could qualify for a fee waiver for their first premarket application. Companies must include gross sales receipts for all their affiliates along with their own gross sales receipts. — Tamra Sami

Medical Device User Fees for FY 2017

Application Fee Type	Standard Fee (as a percent of the standard fee for a premarket application)	FY 2017 Standard Fee	FY 2017 Small Business Fee
Premarket application (submitted under section 515(c)(1) of the FD&C Act, a PDP submitted under section 515(f), or a BLA)	Base fee specified in statute at $268,443, but multiplied by 87.3538 percent	$234,495	$58,624
Premarket report (submitted under section 515(c)(2) of the FD&C Act)	100	$234,495	$58,624
Efficacy supplement (to an approved BLA under section 351 of the PHS Act)	100	$234,495	$58,624
Panel-track supplement	75	$175,871	$43,968
180-day supplement	15	$35,174	$8,794
Real-time supplement	7	$16,415	$4,104
510(k) premarket notification submission	2	$4,690	$2,345
30-day notice	1.60	$3,752	$1,876
513(g) request for classification information	1.35	$3,166	$1,583
Annual Fee Type			
Annual fee for periodic reporting on a Class III device	3.50	$8,207	$2,052
Annual establishment registration fee (to be paid by the establishment engaged in the manufacture, preparation, propagation, compounding, or processing of a device, as defined by 21 U.S.C. 379i(13))	Base fee specified in statute at $3,872, but multiplied by 87.3538 percent	$3,382	$3,382

Source: FDA

FDA Considers How To Use Real-World Evidence for Regulatory Decisions

The FDA is clarifying how it plans to evaluate real-world evidence to determine when it could be used to support regulatory decisions for medical devices.

Real-world data collected from sources outside of traditional trials, including retrospective studies, registries, electronic health records and other sources, could provide enough evidence for regulatory decisions, the FDA said in draft guidance issued July 26.

Although real-world evidence (RWE) gathered from real-world data (RWD) elements could constitute valid scientific evidence, the agency said, it is not changing its evidentiary standards in any way.

Rather, the agency explains how it might consider circumstances under which RWD could be used to support regulatory decisions. For example, an IDE may be needed to prospectively collect and use RWD to determine safety and efficacy. The agency acknowledged that data collected in certain settings may lack rigor compared to data collected in clinical trial settings; however, such data may help inform or augment information about devices that could support approval decisions.

The decision to consider real-world evidence comes alongside the agency's plans to develop a national evaluation system that would leverage RWD to identify safety problems and to better understand risk-benefit profiles (*IDDM*, April 8).

The threshold for considering RWD sources will depend on the device and its level of risk. The guidance discusses which types of data could be useful for gaining additional information. For example, disease-specific RWD sources sponsored by patient advocacy groups could be useful for tracking disease progression for poorly understood diseases. And, treatment-specific RWD could be useful in tracking overall outcomes.

RWE may also be useful for the following applications:

- Generating a hypothesis for a clinical trial;
- As a historical control or as a source of data in a hierarchical model;
- In a registry setting where RWD can be used as a concurrent control group or as a mechanism to collect data related to a clinical study;
- To expand labeling in a broader patient population;
- Conducting post-approval studies;
- In lieu of submitting individual medical device reports; and
- Providing postmarket data in lieu of some premarket data under an expedited access pathway.

RWD could be subject to investigational device exemption regulations if the data collection constitutes a clinical investigation. That determination would be made on a case-by-case basis. If an IDE is required, the FDA would work with the sponsor to determine "the least burdensome approach to facilitate the efficient collection of high-quality data," the guidance says.

Primary factors for considering reliability of data include how the data were collected; whether the data were collected as complete accurate and adequate for answering the specific question studied; and whether people and processes involved in collecting the data provide adequate assurance that the bias is minimized.

To determine whether data accrual ensures reliability; the FDA will assess:

- The preparedness of individual sites for complete and accurate collection of observational data;
- Use of a common data capture form and a common definition framework;
- Data collection procedures and statistical analysis plans;
- Timeliness of data entry, transmission and availability; and
- Whether collecting the data impacts the ability to measure treatment outcomes.

Comments on the draft guidance are due Oct. 25. Read the guidance here: www.fdanews.com/07-27-16-realworldevidence.pdf. — Tamra Sami

EU MDR, *from Page 1*

The changing role of notified bodies will also have an impact on companies. The notified bodies will need to issue new CE marks, and they're going to have to ensure those through testing and regular checks on manufacturers, including unannounced inspections, Meritz said (*IDDM*, Dec. 4, 2015).

Some of the new changes include restrictions on hazardous material such as PVC softeners, and equivalency claims for implantable and high-risk devices will no longer be acceptable. "Companies must conduct clinical investigations and not just rely on equivalency data, which may have been something that you could have done in the past," said Minnie Baylor-Henry, medical devices practice lead at YourEncore.

Stricter requirements on clinical evidence to support assessments of devices will also impact companies.

For example, there will be a requirement that a summary of safety and performance be submitted to the notified bodies for Class III and implantable devices, and this information needs to be publicly available. The agency also expects greater vigilance when it comes to postmarketing reporting, said Baylor-Henry.

Manufacturers will have new deadlines for reporting serious incidents after causal relationships with devices have been established. In the case of a serious health threat, a report needs to be submitted no later than two days after the device-maker becomes aware. In addition, periodic safety update reports will need to be filed annually.

One positive result of this is the extended Eudramed database on devices, which will provide comprehensive information on products available in the EU that will translate into better traceability in the supply chain.

Overall manufacturing operations and supply chain operations will be greatly affected by the new requirements on:

- Labeling. Labels must include the notice: "This is a medical device." Labels must include the unique device identifier, the EU authorized representative and address;
- Reprocessing cycle information required on the label;
- Implant cards for implantable devices. Information must include identification information for the device including UDI and expected lifetime of the device as well as warnings, precautions and instructions for use. The information must be lay friendly and language specific;
- Updated quality manuals and procedures; and
- Recertification for new conformity assessments. Inspections will be more frequent and new technical documentation will be required.

Overall, the new regulations will have a significant impact on the implications around pipelines, and companies should be thinking about the hot spots in their organizations from both a product and function perspective, advised Jon Lange, principal Life Sciences R&D Global Lead at Ernst & Young.

"This really does touch every single part of the business," he said, "and it's not just about implants and Class IIIs. It's really comprehensive. It will affect the products that you market in Europe – every tech file, every label, every one of your core operational processes to some extent or another."

He advises companies to take a worst and best case scenario approach to determine what steps to take and the inherent costs associated with those steps.

There may be a bright spot at the end of all this though. The competitive landscape is likely to change significantly as a result of the new regulations, and there will undoubtedly be acquisition opportunities or alliances with smaller companies that might not be able to comply with the new regs.

Final publication is expected in late 2016 or early 2017. Devices will need to comply within three years; in vitro diagnostics will have five years to comply. — Tamra Sami

UDI Guidance Covers Testing, Other Considerations

Companies labeling products with unique device identifiers should test the automatic identification form of the UDI to make sure it can be reliably scanned by the appropriate technology.

The FDA clarified expectations on unique device identifiers, which must appear in two forms on device labels and packages: an easily readable plain-text form and an automatic identification and data capture technology form, a new FDA draft guidance says.

If a labeler chooses a bar code form of AIDC, it should also be tested for print quality, accounting for the expected handling and use life of the device. Labelers should discuss print quality requirements with their FDA-accredited issuing agency.

If a labeler uses more than one type of AIDC technology form, there should still only be one plain-text form on the label, and it should be near one of the AIDC forms.

Use AIDC Form As Much as Possible

The AIDC form should be used as much as possible to cut down on errors from manually entering the information. This form can be split into multiple segments and should be readable with a bar code scanner or other AIDC technology.

If the AIDC form is not visible to the human eye, the label or device package must disclose the presence of AIDC technology, the guidance notes.

The plain-text form can be used as a failsafe if the AIDC form cannot be scanned or used, the guidance says. It should include the device identifier, up to five production identifiers and data delimiters from the UDI. It can have multiple lines of text and should be below or near the AIDC form.

Data delimiters are a defined character or set of characters that indicate and precede specific data elements, such as the device identifier or production identifiers. They will vary

(See **UDI***, Page 8)*

FDA Updates Guidance on Adaptive Designs for Device Studies

FDA provided additional details for sponsors on how they should go about designing adaptive trials for medical devices.

The guidance, released July 27, makes several updates to draft guidance that was released on May 18, 2015.

The updates take into account comments the agency received that centered on definitions and particulars, but the updated guidance is not substantively changed from the draft document (*IDDM*, May 15, 2015).

Some of the changes in the updated guidance include additional examples of modifications for prospectively-planned adaptive study designs. The agency stresses that adaptive trials focus on anticipated changes based on accumulating data.

The most important consideration is whether an adaptive design is feasible and whether an adaptive design is more appropriate than conventional designs, the FDA said. The agency provides suggestions on how to decide if an adaptive design is advantageous, and it provides more detail on various scenarios to make that determination.

The document lays out the principles for adaptive trials and how sponsors need to control the chance of erroneous conclusions and to minimize operational bias. Both of these factors can be a "significant threat" to the scientific integrity of a clinical study and can't be overcome by statistical adjustments, the agency warns.

Different adaptive trial designs are explained in detail, including group sequential designs, sample size readjustment, Bayesian sample size adaptation, dropping a treatment arm, changing the randomization ratio, and investigating both superiority and non-inferiority adaptive enrichment.

The agency received comments from six organizations, including AdvaMed, which praised

(See **Design***, Page 6)*

Low-Risk, *from Page 2*

Examples of general wellness devices include those that make claims related to weight management, physical fitness, relaxation or stress management and sleep management.

However, devices that make claims to treat or diagnose obesity or to treat an eating disorder would not fall under the scope of the guidance.

Examples of devices that fall under the second category include software that teaches breathing or relaxation techniques that might help reduce migraine headaches, or software that tracks and records sleep, work and exercise to help people living with anxiety.

Examples of products that are not low risk would include sunlamp products, implants for improving body image, or a laser product that claims to improve confidence by rejuvenating the skin.

Read the guidance here: www.fdanews.com/07-29-16-lowriskdevices.pdf. — Tamra Sami

Design, *from Page 5*

the agency for the document, and provided an eight-page attachment that highlighted line item changes it wanted, including examples of adaptive designs for diagnostic devices. In response, a new section provides more information on adaptive studies for diagnostic devices.

The agency also received comments from Cook Medical Group, which noted that the agency should clarify when trials should be stopped early for futility. It also suggested the agency provide clarity on when adaptive designs may not be feasible.

The guidance also goes into detail on special considerations such as changes to pivotal trials that are not preplanned using blinded data and unblinded data. Challenges of adaptive designs are highlighted as well, and the agency stressed the importance of data monitoring committees and IRBs, techniques to minimize operational bias and logistical challenges.

Read the updated draft guidance here: www.fdanews.com/07-27-16-AdaptiveDesignsGuidance.pdf. — Tamra Sami

J&J's Acclarent Pays DOJ $18 Million To Settle False Claims Allegations

Johnson & Johnson subsidiary Acclarent will pay $18 million to resolve false claims allegations related to its sinus spacer product.

The DOJ alleged that the company caused healthcare providers to submit false claims to Medicare by marketing and distributing the drug-delivery device without FDA approval.

Acclarent markets devices used in sinus surgeries, including the Relieva Sratus MicroFlow Spacer. The FDA cleared the company to market the device with saline to keep sinuses open following surgery.

But the DOJ alleged that Acclarent used the product as a drug-delivery device for corticosteroids.

Moreover, Acclarent marketed the Stratus as a drug-delivery device even after the FDA rejected the company's 2007 request to expand the approved uses, the DOJ said, noting that "Acclarent employees trained physicians using a video that demonstrated the Stratus being used with prescription corticosteroid Kenalog-40."

In May 2013, Acclarent discontinued all sales of the Stratus in the U.S., and the company agreed to withdraw FDA marketing clearances.

Former Acclarent CEO William Facteau and former sales VP Patrick Fabian were convicted of 10 misdemeanor counts of introducing adulterated and misbranded devices into interstate commerce, the DOJ said.

The civil settlement resolves a lawsuit filed under the whistleblower provision of the False Claims Act filed in the District of Massachusetts.

J&J told *IDDM* that this was a civil-only resolution, "with no admission of any liability, or wrongdoing. The alleged conduct took place almost entirely prior to the acquisition of Acclarent in 2010 and immediately after the acquisition, Johnson & Johnson introduced numerous compliance changes to Acclarent." — Tamra Sami

BRIEFS

FDA Issues Mammography Notice

When mammography facilities are found to be noncompliant with quality standards, the FDA can require the facility to perform a patient and provider notification.

The facility will receive a letter citing the reasons for the PPN action and instructions to complete to become compliant, the FDA said in a notice issued July 27.

The facility is assigned a compliance officer to guide it through the actions it needs to take to become compliant. The agency will then track the notification procedures and audit the facility. Read the notice here: www.fdanews.com/07-27-16-mammographyinspections.pdf.

Carefusion Recalls Laparoscopes, Ventilators

Carefusion issued an urgent recall of several of its laparoscopes, including the DiamondFlex circular retractor and the SnowdenPencer.

The Class I recall was issued because BD, formerly Carefusion, identified a weld failure that could result in the wire protruding through the tip of the instrument, which could damage tissues or organs. Customers were instructed to return the affected devices.

The same week, the company turned around to issue another Class I recall for its AVEA ventilators due to an electrical issue that could cause the device to shut down unexpectedly.

The AVEA recall affects 501 units distributed in the U.S.

Reports of Catheter Breakage Triggers Recall

Stryker Sustainability Solutions announced that it was recalling 167 Soft-Vu Omni Flush Angiographic catheters following reports of the product top breaking off during usage.

The recall, which the FDA designated a Class I recall, affects products distributed in 11 states between January 2004 and December 2008.

(See **Briefs**, *Page 8)*

UDI, *from Page 5*

based on the FDA-accredited issuing agency, so these agencies should submit their proposed data delimiters to FDA as part of their accreditation application, the guidance says.

While some of the issuing agencies may allow non-UDI elements, such as quantity, in the UDI carrier, the FDA does not recognize these as being part of the UDI. Therefore, UDI elements must be distinguishable and able to be captured separately from non-UDI elements. Additionally, the UDI elements should precede any non-UDI elements.

The plain-text form of the UDI should list the DI first, followed by any production identifiers. Any non-UDI elements in should follow the production identifiers.

The UDI rule does not require that any of the five production identifiers be listed on the label, and some Class I devices may have a UDI that includes a DI only. But "it is important to note that for other than Class I devices, if one or more of the five PIs defined under 21 CFR 801.3 are included on a device label, the UDI must include each of the PIs that appears on the label," the guidance says.

It adds that one UDI can be presented in two linear bar codes: one for the DI followed by another for the production identifiers. These should be near each other on the device label, packages and/or device.

The draft guidance is available at www.fdanews.com/07-26-16-UDIguidance.pdf. Comments to the guidance are due by Aug. 27.
— April Hollis

Briefs, *from Page 7*

Tip separation can lead to internal organ injury and multiple other serious adverse events.

SPR Therapeutics' PNS Cleared

SPR Therapeutics has received clearance from the FDA to market the Sprint Peripheral Nerve Stimulation (PNS) system.

This pain management device allows lead placement as far as two to three centimeters from the intended nerve.

The PNS is fully reversible, as the device is designed to be removed without surgery at the end of the 30-day treatment period.

Itamar's C-PAP Gains Indication

Itamar Medical received FDA clearance to expand the indication of their sleep apnea diagnostic device to include younger patients.

The tool is now approved for use in patients as young as 12. It previously had been approved only for use in patients 17 and older.

Similar approvals already have been granted in Europe and Japan.

Canada Approves Edwards' Heart Valves

Health Canada has approved Edwards Lifesciences' heart valve Edwards Sapian 3 for use.

The product is approved for use in patients who suffer from symptomatic aortic stenosis and are at high risk for surgical replacement.

Edwards' new valve is available in four sizes: 20 mm, 23 mm, 26 mm and 29 mm.

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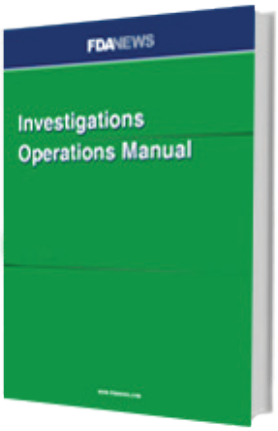

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