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IN THIS ISSUE

House Panel Adopts 21st Century Cures Act With Third-Party Audit Provision

The House Energy & Commerce Committee's health subcommittee Thursday voted unanimously to approve the latest version of the 21st Century Cures Act, which aims to reduce the regulatory burden on devicemakers through third-party audits while accelerating the development of novel treatments.

The vote confirms a provision, included in Wednesday's third discussion draft, allowing FDA-accredited third parties to conduct inspections related to relatively minor device design changes, such as those made under 30-day supplements or special PMA supplements. They would not replace FDA investigators for more broad regulatory inspections.

Following an assessment, the FDA would have 30 days to review the results before they were considered final, the measure says. Third parties would be paid by the devicemakers who hired them, not by the FDA. The subcommittee made no changes to the measure

(See **21st Century Cures**, *Page 2)*

Draft Guidance Gives Devicemakers More Flexibility in Clinical Trials

Sponsors considering whether to use an adaptive design for their device clinical trial should select a number of realistic scenarios and determine how likely each is to succeed with a particular adaptation, the FDA says.

This exercise should be conducted during the planning of the pivotal study, according to draft guidance released Friday on adaptive designs for medical device clinical trials.

The guidance is meant to make it easier for sponsors to adjust ongoing trials in the face of new information or unexpected outcomes. Adaptive designs can also enhance devicemakers' understanding of a product's benefits and risks and ease the transition from premarket investigation to postmarket follow-up, the FDA says.

The idea has gained traction in recent years as a way to reduce trial costs and increase the odds of a study's success.

(See **Adaptive Designs**, *Page 4)*

21st Century Cures, *from Page 1*

The bill's third-party audit provision hews closely to the ongoing Accredited Persons Inspection Program, which was first authorized as part of device user fee legislation in 2002. That pilot program allows the FDA to recognize third parties to assess the quality systems of eligible devicemakers, determine compliance with existing regulations and report their findings back to the FDA, which then makes the final compliance assessment.

Success in a third-party audit replaces a regular FDA inspection. The agency has accredited 14 bodies to perform inspections. The FDA would be required to issue draft guidance on the 21st Century Cures third-party program within 12 months of the measure's passage, followed by final guidance no more than a year later. A report evaluating the third-party program's results would be due in 2022.

The measure replaces a late April version that had dropped third-party audit language (*IDDM*, May 1). The measure adopted by the subcommittee also would establish a breakthrough pathway for innovative devices, allow for a broader range of data to be considered in device approvals, require new guidance on the least-burdensome provision and on the use of recognized standards in the device approval process, and set rules limiting the FDA's ability to regulate software as a medical device.

The full committee will consider the measure, which has not been assigned a bill number, next week, and the plan is to get a bill to the House floor by June and have it on the president's desk by the end of the year. There is no comparable measure in the Senate.

View measure at www.fdanews.com/05-14-15-third-draft.pdf. — Elizabeth Orr

Health Canada Response Times Surpass Own Deadlines by Days

Health Canada exceeded its review targets for device submissions during the 2015 first quarter, reviewing new Class II devices in an average of nine days, six days quicker than the 15-day goal, and completing Class IV device reviews in an average of 70 days versus a 75-day goal.

About 65 percent of all decisions were made a week or more ahead of deadline, the agency reports. The agency received 784 new Class II applications during the period, up from 730 in the same period a year ago. The number of Class III and Class IV submissions dipped slightly—from 274 to 236 and from 94 to 86, respectively.

Fifty-nine percent of applications processed during the quarter were deemed complete on the first round. Another 29 percent required only one request for additional information, with only 12 percent needing two or more rounds of follow-up, the agency says. The most common reasons for information requests for Class III and IV devices were safety and effectiveness studies, labeling and documentation, background information and marketing history or regulatory status.

The most frequent screening deficiencies were similar: safety and effectiveness studies, background information, fees, labeling and documentation, manufacturing quality controls and licensing.

For devices other than in vitro diagnostics, marketing history and regulatory status also cropped up as common deficiencies. Only 10 percent of applications were considered to have poor-quality data.

The Health Products and Food Branch inspectorate received more than 400 reports of adverse events in the 2014 third quarter, the last for which data is available.

About 300 of these resulted in recalls, Health Canada says. General hospital products generated the highest number of reports, with plastic surgery and anesthesiology devices also frequently implicated.

The most common observations during inspections involved establishment licensing and complaint handling, the agency says.

View the report at www.fdanews.com/05-18-15-canada.pdf. — Elizabeth Orr

Overhaul of Clinical Trials Program Aims for Speed, Consistency: FDA

The U.S. FDA's device center is taking steps to improve the predictability of IDE reviews with the establishment of a new director-level position to oversee the clinical trials in the Office of Device Evaluation, a center official says. The change, part of a broader reorganization within ODE, will also establish new procedures for the director's involvement in IDE decisions and a focus on exercising flexibility where appropriate, ODE Deputy Director Barbara Zimmerman told Medcon 2015 in Cincinnati, Ohio.

Staff involved in reviewing IDEs will report to the trials director once the reorganization is complete, Zimmerman said. In addition, ODE is designating managers as feasibility study directors. Sponsors planning an early study should contact the office directly to find out who their director will be, she said.

By the end of June, the device center hopes to reduce by 50 percent the number of IDEs requiring more than two cycles to be approved and reduce the overall median time for approval to 30 days. Companies whose trial proposals are rejected would hear from the agency within 10 days.

The changes are intended to strengthen the center's clinical trial program, improve efficiencies and predictability in the IDE process and increase the number of early feasibility/first-in-human IDE studies conducted in the U.S., Zimmerman said.

Quynh Hoang, a former FDA official and senior regulatory consultant at King & Spalding, said firms going through any form of presubmission process should willingly accept FDA advice.

Hoang also suggests devicemakers include page numbers for easy reference in the acceptance checklist as a way to help build a good impression. She also advises companies that get requests for information from trial results to specifically address the question, rather than pointing to where information might be found in appendixes to the original application. — Elizabeth Orr

Australian Fee Change Plan Benefits Some Devicemakers

Australia's Therapeutic Goods Administration is proposing changes to its low-value turnover exemption scheme that could help some devicemakers save money while reducing red tape and making the process more user-friendly and transparent.

The government levies annual charges to recover the costs of certain regulatory functions for medical devices and other products listed on the Australian Register of Therapeutic Goods.

The current scheme allows firms to avoid those charges if their annual sales turnover is less than or equal to 15 times the fee. Because of the burden involved in preparing and submitting an application, some companies are discouraged from seeking the exemption, the TGA says.

Under the revised scheme, the exemption would be replaced by an annual charge exemption, or ACE. Devicemakers could self-declare that they had zero dollars of sales turnover in the previous fiscal year to qualify for the exemption, rather than having to obtain a third-party accountant's certification. The government would conduct audits to detect incorrect declarations.

The new scheme would simplify the exemption process for devicemakers and the TGA by eliminating applications and application fees and not requiring approval by a delegate of the health secretary, the TGA says.

The Federal Executive Council is expected to consider the proposal before June 30, says TGA spokesman Neil Branch. Once approved, the agency will provide guidance to industry.

Starting next month, the TGA plans to inform devicemakers of eligibility for an initial ACE, with plans to implement the scheme on July 1. Sponsors would be required to self-declare on an annual basis between July 1 and July 22 starting next year. Annual charges would be due Sept. 15.

Read the regulation impact statement and Q&A document at www.fdanews.com/5-15-TGA-ACE.pdf and www.fdanews.com/5-15-TGA-ACE-QA.pdf, respectively. — Jonathon Shacat

U.S. FDA Outlines Use of Patient Preferences in Device Approvals

The U.S. FDA is making good on promises to consider patient preferences in device approvals, draft guidance issued Thursday makes clear.

The 32-page document discusses the main factors sponsors and other stakeholders should consider when collecting patient preference information that may be used in the premarket review of PMAs, HDE applications and *de novo* requests. While submitting the information is optional, it can assist the FDA in assessing a device when multiple treatment options exist and none is clearly superior, or if patients' views on a product's benefits and risks are significantly different from those of healthcare providers.

Information on patient preferences may be especially useful with devices that are directly used by patients, devices intended to yield significant health and appearance benefits and life-saving, but high-risk devices, the FDA says. Devices that include novel technology or are designed to fill an unmet need may also benefit from patient preference studies, the agency adds.

Patient preference studies should incorporate the following:

- A representative patient sample with results that can be generalized;
- Differences in patients' preferences, including those shaped by disease severity, patient age and personal risk tolerance;
- Good clinical practices;
- Effective communication of the benefit, harm, uncertainty, and risk to patients, through such techniques as presenting information in multiple formats and avoiding fractions when comparing risk levels;
- Designing the study to minimize cognitive bias;

(See **Patient Reference***, Page 8)*

Adaptive Designs*, from Page 1*

Typically, modifications should be identified before a trial begins and described in the protocol. But modifications made during a trial may be scientifically valid if designers don't know the outcomes, FDA says. The guidance applies to all trial stages and all device applications.

Sponsors that choose to use adaptive designs need to focus on two key goals — controlling the chance of erroneous conclusions and minimizing operational bias, the FDA says. This means understanding the chances of false positive and false negative conclusions and the effect of multiplicity on results — e.g., analysis of multiple endpoints or subgroups.

To avoid the risk of false results, the FDA recommends sponsors use analytical methods and simulation studies that make it easier to spot errors. To minimize bias, it is critical that sponsors and investigators don't have access to unblinded results during an ongoing trial, the agency adds.

The guidance describes 11 types of study adaptations. Among these are:

- Group sequential design, in which an interim analysis of treatment outcomes is done so the study can be stopped for success or futility, if necessary;
- Sample size adaptation. While adding more patients to improve the results of a failed trial is not scientifically valid, adaptive design techniques can be used to allow for an extension that minimizes the chance of errors, the FDA says;
- Dropped treatment arm based on poor effectiveness;
- Revised randomization ratio. This can improve study efficiency and protect patients by directing more subjects to a treatment that has been found to have better outcomes;
- Unplanned changes to the device or

(See **Adaptive Designs***, Page 8)*

Smith & Nephew Warned Over Issues Related to Morcellators

The FDA hit Smith & Nephew with a warning letter for quality, CAPA and procedural issues related to its Truclear Ultra Reciprocating Morcellators 4.0.

The devicemaker placed a voluntary hold on shipments of the morcellators following a March 26 Form 483. The product will remain on hold until Smith & Nephew completes its enhancement of quality systems documentation for the product, company spokesman Joe Metzger tells *IDDM*.

During a March 4-26 inspection of the firm's Andover, Mass., facility, investigators cited failure to establish and maintain procedures for verifying or validating corrective and preventive actions following complaints of loss of visualization when using the Truclear Ultra Reciprocating Morcellators. Eight corrective action reports reviewed during the inspection lacked sufficient information to ensure the issue was resolved, the April 30 warning letter says.

Smith & Nephew continues to receive complaints about the product more than two years after a review began in September 2012. The company placed a hold on the morcellator in August of that year, but it was removed before the review of the complaints was completed — a violation of the firm's procedures.

Other violations observed during the inspection included failure to establish procedures to control nonconforming product, failure to establish and maintain procedures to verify device design, and failure to establish procedures quality audits.

The FDA asked for an update regarding improvements Smith & Nephew is making to its CAPA system, including having a quality manager oversee the revised system. Metzger says the company is working with the FDA to resolve all issues.

There have been no FDA-issued field actions, recalls or seizures as a result of the warning letter, he says.

Read the warning letter at www.fdanews.com/05-12-15-SmithNephewWarning.pdf.
— Kellen Owings

EMcision Recieves Warning Letter for Inadequate CAPA Procedures

British devicemaker EMcision received an FDA warning letter for medical device reporting failures, inadequate CAPA procedures and other issues.

According to the Nov. 20 warning letter posted online Tuesday, the company failed to develop, maintain and implement written MDR procedures. For example, the procedures omit the definition of the term "become aware," which could result in an incorrect decision when evaluating a complaint to see if it meets reporting criteria. The company also failed to specify who on staff decides to report events to the FDA, the letter says.

EMcision's procedures also lack instructions for completing MDRs in a timely matter and for how documentation and record-keeping requirements will be addressed, the letter adds. In an Aug. 29 response to a Form 483, EMcision said it would revise its MDR procedure and submit a copy, but the agency never received one, the letter says. The warning letter followed an Aug. 11 to 14, 2014, inspection.

EMcision also failed to maintain complaint files, process complaints in a uniform and timely manner, document oral complaints and evaluate them to determine if they needed to be reported to the FDA.

Investigators reviewed all eight CAPAs initiated between 2009 and 2013 and found that all were missing some documentation, contained conflicting information or had no signatures, the warning letter says.

Further, the company failed to follow document management procedures and didn't establish and maintain procedures for identifying, documenting and validating design changes for its Habib EndoHPB endoscopic bipolar radio frequency probe.

EMcision did not return a request for comment by press time. The warning letter is available at www.fdanews.com/05-14-15-EMcision.pdf. — Kellen Owings

Duodenoscope Superbug Cases May Be Due to Human Factors, Panel Says

Panelists and stakeholders at an FDA advisory panel meeting on infectious outbreaks linked to improperly cleaned endoscopes struggled to find ways to enhance device safety while staying within the limits of FDA authority.

The Gastroenterology and Urology Devices Panel met Thursday and Friday to discuss possible ways to improve the safety of duodenoscopes, which have been tied to ongoing outbreaks of antibiotic-resistant bacteria. The agency issued final guidance tightening device reprocessing rules in March after at least 135 cases of suspected superbug transmission were reported between January 2013 and the end of last year (*IDDM*, March 13).

Most of last week's discussion focused on the need for proper cleaning and sterilization, rather than just disinfecting the devices, to kill bacteria causing the infections. FDA chemist Elaine Mayhall noted that ethylene oxide sterilization, which kills at least 12 types of bacteria, is used on other hospital equipment and has never been associated with a superbug outbreak.

Kenneth McQuaid, with the Veterans Affairs Medical Center in San Francisco, suggested that the FDA conduct a review of hospitals' duodenoscope cleaning policies and training. Licensing technicians or requiring validation at the end of the cleaning process could help, he said.

While that might help, Benjamin Fisher, director of CDRH's Division of Reproductive, Gastro-Renal and Urological Devices, pointed out that the FDA has no authority to regulate hospitals and can't dictate how technicians should be trained to reprocess equipment.

Eight patients became infected and three died at UCLA Ronald Reagan Medical Center in Los Angeles earlier this year. — Elizabeth Orr

Expert: European Council Likely To Release Device Regs in June

Devicemakers should expect to see the European Council's final version of the proposed medical device and in vitro medical device regulations next month, an EU industry official says.

John Brennan, director of regulations and industrial policy at MedTech Europe, says there's a 90 percent chance the Council will wrap up its three years of confidential talks and sign off on the proposal next month. If that happens, the proposal would go to the health minister on June 19.

Once the health minister has the two documents, the European Parliament, Council and the European Commission will work to finalize the regulations. Each body has created its own draft and the Council's is the last to be released. Brennan, who provided the update at MedCon 2015 in Cincinnati, Ohio, expects the regulations to be enacted in the first half of 2016.

The negotiations have been tricky because each of the EU's 28 member states must agree to implement the regulations to the letter of the law, Brennan says. Previously, countries could tweak EU recommendations on device regulation to fit local conditions.

Key changes include increased traceability requirements, better central control over notified bodies and a stricter approach to hazardous materials used in devices. The proposed regulations would impose an immediate four-year ban on any manufacturer found to use hazardous substances, but Brennan says that will be stepped down to a sensible and science-based approach the industry would support.

Changes to IVD regulations, including requests for clinical evidence that rise to near-pharma level, may cause the most challenge, Brennan says. "The whole IVD discussion is being overshadowed by the device discussion."

Another concern, he says, is that the current versions of the regulations don't properly differentiate requirements that would be imposed on Class III devices from requirements for all devices. That could lead to problems if the stricter standards are imposed sector-wide, Brennan says.

Industry would also like to see more forward motion on unique device identifiers throughout Europe, Brennan says. The concept of using UDIs to build a centralized database is widely supported, but has been stymied by inaction at all levels, he says. — Elizabeth Orr

NICE Would Expand Devicemaker Input on Technology Assessments

Devicemakers should be at the table when rules around interventional procedures are developed, the UK's health cost watchdog recommends.

According to the National Institute for Health and Care Excellence, two-thirds of interventional procedures involve medical devices, but manufacturers can observe and comment on NICE committee work only as members of the public. Conversations with trade groups convinced NICE that a more formal interaction would benefit both the agency and industry by bringing more evidence and information to the technology assessment discussions.

NICE proposed the heightened collaboration in a draft update to its Interventional Procedures Programme Manual released May 8.

The revised manual would allow NICE to identify devicemakers as possible interested parties while guidance documents are being drafted and ask them for information that could help guide the development process. This might include company data, planned trials and the names of hospitals using specific devices. In addition, the companies would attend committee meetings to answer questions about their products that could help with the assessment.

Comments on the draft manual are due July 31, and a final version will be released in February 2016. View the draft at www.fdanews.com/05-18-15-interventional.pdf. — Elizabeth Orr

Patient Reference, *from Page 4*

- Critical aspects of risk, benefit and uncertainty in preferences over several relevant clinical domains;

The FDA tasks sponsors with keeping accurate case histories, including include patient diaries, assessments and other electronic patient-reported outcome tools.

The FDA anticipates using patient preference information throughout the device lifecycle, from influencing device design and shaping clinical trials to factoring into postmarket monitoring.

Companies that plan to collect patient preference information should meet with Center for Devices and Radiological Health staff early in the trial design process, the agency says. Patient preference information may be submitted as part of a PMA or other application or by an academic or patient group.

View the draft guidance at www.fdanews.com/ext/resources/files/05-15/05-18-15-preference.pdf. — Elizabeth Orr

Adaptive Designs, *from Page 1*

The FDA recommends against the use of adaptive designs in trials that enroll patients so quickly that all the results are obtained at about the same time, giving designers little chance to make changes based on interim data. The agency also discourages them in complex studies that have multiple primary or secondary endpoints.

Sponsors submitting an adaptive trial design should explain the proposed adaptation, including what, when, how and why the adaptation will be performed.

The guidance was one of several promised on the FDA's 2015 priority list (*IDDM*, Jan. 9).

View the guidance at www.fdanews.com/05-18-15-adaptive.pdf. — Elizabeth Orr

BRIEFS

BSX Settles Another Mesh Lawsuit

Boston Scientific has settled another lawsuit involving allegations that its Pinnacle transvaginal mesh product harmed a patient while using it. The confidential settlement, reached May 11 in a U.S. district court in California would have gone to trial this week—the sixth against Boston Scientific over the device. The Marlborough, Mass., devicemaker, which is facing more than 26,000 liability lawsuits claiming the urinary incontinence device is defective and causes complications, plans to pay an estimated $119 million to resolve nearly 3,000 cases.

Cryoablation System OK'd in U.S., EU

Medtronic's Arctic Front Advance ST cryoablation catheter has won FDA approval for the treatment of patients with drug refractory, recurrent, symptomatic paroxysmal atrial fibrillation. It also earned a CE mark for use in patients with atrial fibrillation, a wider indication than its American counterpart. The device is part of the Arctic Front Advance System, the only cryoballoon system to have the above indications in the U.S. and Europe. Medtronic plans a limited release followed by a wider launch this fall.

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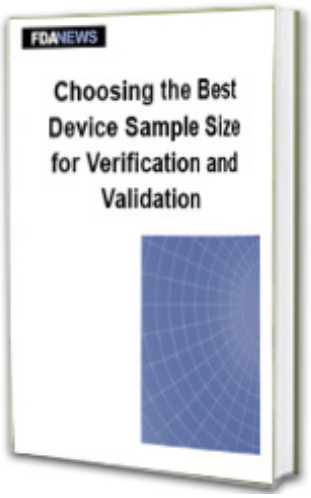

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