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IN THIS ISSUE

AdvaMed Amicus Brief Urges Supreme Court to Review 510(k) Verdict

AdvaMed filed an amicus brief asking the U.S. Supreme Court to overturn a jury verdict against J&J subsidiary Ethicon dealing with pelvic mesh devices — in a case that featured the admissibility of evidence from a 510(k) review.

In the January decision, the U.S. Court of Appeals for the Fourth Circuit upheld a $3.27 million district court judgment in favor of plaintiff Jo Huskey, who claimed severe pain from use of pelvic mesh devices manufactured by Ethicon. The Fourth Circuit upheld the district court's exclusion of all evidence of the Ethicon device's 510(k) clearance.

Decisions to exclude this evidence "prevent juries from hearing the full story, which is fundamentally unfair," said AdvaMed's legal committee chair, Ann Bunnenberg, president and COO of Electrical Geodesics.

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

EU Regulators Affirm That Cranberry Products Are Not Medical Devices

An EU committee approved the European Commission's decision that cranberry products are not medical devices — in a decision with broader implications for "borderline" situations where a product's primary mode of action is unclear.

The so-called "Cranberry Decision" ruled that cranberry products with a primary intended action based on proanthocyanidins and used for cystitis treatment or prevention do not constitute devices. The European Commission issued its draft decision in February 2016, and formal adoption of the decision is expected later this summer.

The European Medical Association's Committee for Medicinal Products for Human Use reviewed the draft decision, the scientific

(See **Cranberry**, *Page 2)*

510(k), *from Page 1*

The Fourth Circuit contravened the FDA's position that the 510(k) process is guided by principles of safety and efficacy, according to the brief. The court said the clearance information held little relevance regarding the device's safety because the primary focus of the 510(k) pathway is the equivalence between the device in question and an older device.

In the brief, AdvaMed argues the court's finding relies on outdated information. The ruling cites a 1982 decision, while AdvaMed cites FDA materials from 2014 and 2017 emphasizing the role that evidence of safety and efficacy plays in the 510(k) review. In addition, the group writes, the importance of these principles in the equivalence determination process has been the FDA's "consistent position" since the 1990 Safe Medical Devices Act.

The brief calls on the Supreme Court to review the earlier decision and clarify whether it is lawful to bar devicemakers from citing FDA clearance as a defense against claims the product is unsafe.

Read the AdvaMed brief here: www.fdanews.com/06-28-17-Brief.pdf.

Read the Fourth Circuit's decision here: www.fdanews.com/06-29-17-Appeal.pdf. — Zack Budryk

Cranberry, *from Page 1*

literature and previous EC guidance and concluded that a mechanical mode of action of proanthocyanidins is "highly unlikely." The products are most likely properly classified as pharmacological, according to the committee.

The ruling is part of a larger debate over borderline issues. The EC issued guidelines on the topic to aid regulators in making classification decisions.

Three years ago, France's medical product regulator revoked manufacturer Arkopharma's Class IIb EU medical device status for cranberry-based products, with the regulator claiming it lacked the data to justify the designation.

The decision echoes controversy over the classification of combination products by U.S. regulators. Device advocates argue the FDA holds a bias against devices during the classification process, and automatically classifies any combination product involving a chemical reaction as its primary mode of action as a drug.

While the Cures Act attempted to address this by establishing that a chemical reaction alone does not make a product a drug, an additional legislative solution is necessary, according to David Fox, a partner with Hogan Lovells and a former counsel to FDA's combination products programs and former associate chief counsel for drugs (*IDDM*, April 25).

Read the EMA committee's decision here: www.fdanews.com/06-30-17-Cranberry.pdf. — Zack Budryk

How to Manage Risk in a World of Changing Design Control Standards

How does the changing landscape of international standards overlap with design control, and how should devicemakers account for these changes in their risk management plans?

One place to start is the model for risk management developed by the International Medical Device Regulators Forum (IMDRF), said Ombu Enterprises President Dan O'Leary during a recent FDAnews webinar. FDA investigators use this model as part of their training, he added.

About 10 percent of all FDA warning letters cite risk management deficiencies, and about 55 percent cite design controls. How devicemakers relate their activities in risk management with their activities in design controls and how those processes interact with each other is the core of any medical device manufacturing risk management plan.

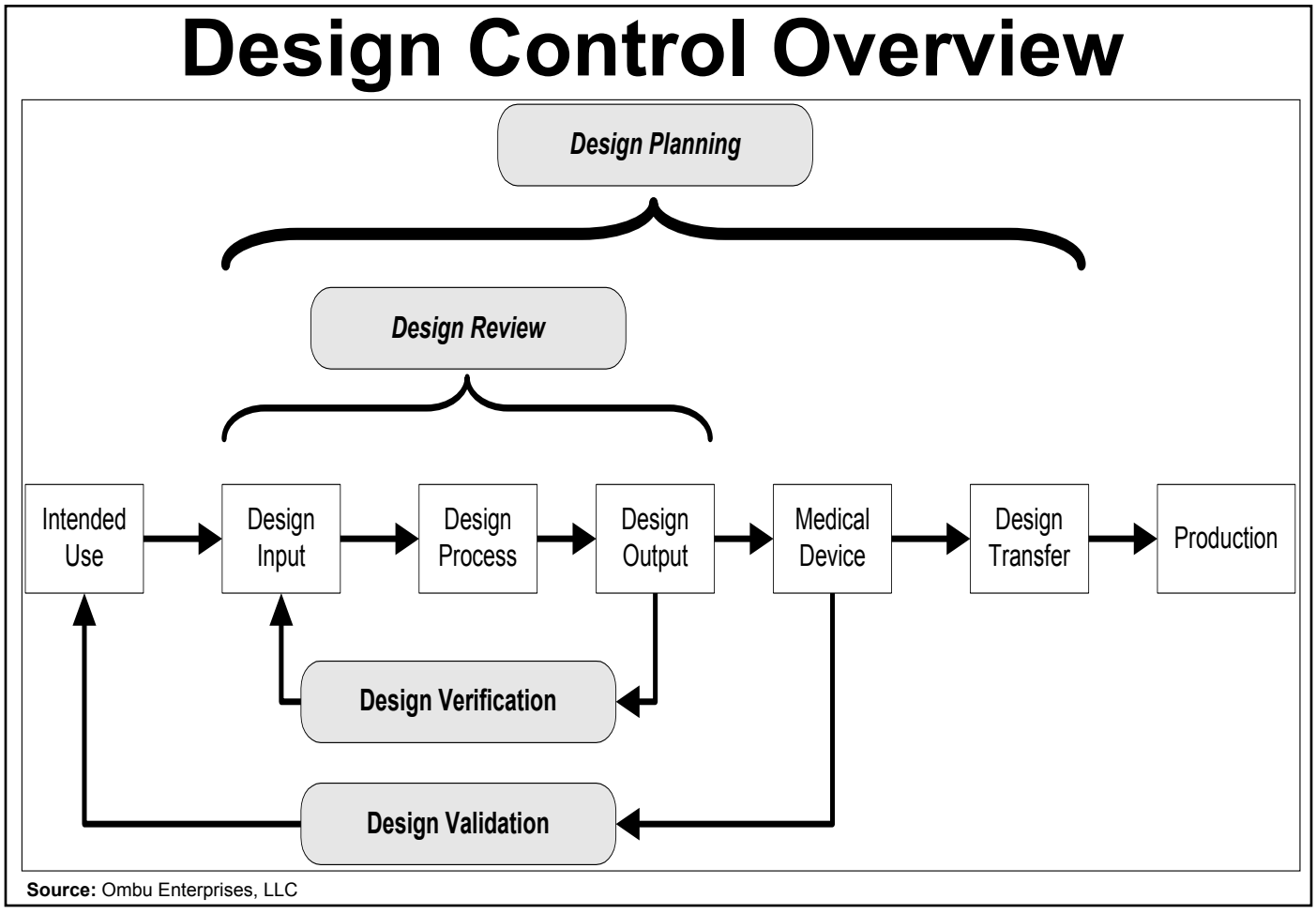
Quality managers should examine the most common standards to better understand the overall landscape.

The international quality management standard is ISO 13485:2016, and ISO 14971:2007 is used for risk management. There are, however, some regional differences. In the U.S., FDA follows 21 CFR Part 820, the quality system regulation, for quality management. For risk management, the FDA recognizes the international version, ISO 14971:2007, and the corresponding U.S. version, that uses the ANSI/AAMI acronym.

Canada uses the 2003 version of ISO 13485, but it's moving toward the 2016 version as part of the Medical Device Single Audit Program certification.

The European Union has made some modifications that will align with the current device

(See **Design***, Page 4)*



Source: Ombu Enterprises, LLC

Design, *from Page 3*

directives in the European Union, which are indicated by the "EN" prefix, such as EN ISO 13485:2012 and EN ISO 14971:2012.

For design controls, devicemakers should begin by understanding the intended use of a device from a user perspective. This analysis will provide important data the design engineers will use for the design output, which forms the basis for the device master record that documents the production process.

Design validation will verify whether the device satisfies the intended use. Intended use also is going to be an element of risk management and "it's going to help us understand what the basic issue is going to be in risk management," O'Leary said. "We're going to analyze all of the ways in which our medical device could harm the patient or user."

"Design verification is also going to play an important role in our risk management strategy. In design verification, I'm going to document the method by which I did the verification, when I did it and who was involved."

A risk analysis then looks at the process steps to identify ways in which a device could harm the patient. Although some risks might arise because the device fails, different risks might arise when the device is operating normally.

By estimating the severity and probability of harm, a company can estimate the risk, and then decide whether the risk is acceptable or not. In the risk management plan, the acceptability criteria are further evaluated to decide whether risk reduction activities are needed.

"Basically, I'm going to take my risk estimate, and I'm going to compare it with the acceptability criteria that I documented in the risk management plan," O'Leary said.

This process will lead to three possible outputs:

- The risk is acceptable because it's negligible;
- The risk is acceptable with risk minimization; and
- The risk unacceptable.

Risk control measures are then implemented and verified. "I'm going to look at the residual risk, and the risk left over after risk control measures were implemented. If it's not acceptable, then I'm going to go back and try additional risk control measures until I get it to be acceptable."

Access the webinar, Device Design Control and Risk Management, here: www.fdanews.com/products/54340.

PEOPLE ON THE MOVE

HYCOR Biomedical, a manufacturer of in vitro diagnostic devices, announced the appointment of four new members to its senior management team, including **Eric Whitters** as COO, **Tommy Chiu** as vice president of operations, **Ulf Bladin** as vice president and general manager for EMEA territory, and **Kim Walker** as vice president of regulatory, quality and clinical affairs.

Baltimore-based image-fusion medical device manufacturer **Clear Guide Medical** has named **Bob Cathcart** as its new chief executive officer. Cathcart, who most recently served as senior vice president of global sales at Hansen Medical, has more than three decades of experience in the medical device field. He will succeed Clear Guide co-founder Dorothee Heisenberg as CEO. Heisenberg will remain with the company as executive vice president.

Lumicell has appointed **Felix Geissler** as its new chief medical officer. Geissler most recently served as medical head for the oncology department at Sanofi Genzyme and has previously worked for Novartis and BMS and as a transplant surgeon at the University of Wisconsin Hospital in Madison. He will collaborate with the imaging company's R&D and marketing departments to develop its overall business strategy.

483 Roundup: FDA Cites Five Devicemakers for Procedural Failures

Five device manufacturers landed Form 483s from the FDA over their handling of complaints, medical device reporting, and corrective and preventive actions, among other deviations.

Peter Schiff Enterprises: The FDA issued a Form 483 to Peter Schiff Enterprises, citing validation issues, incomplete records and inadequate procedures.

The agency issued the form after an April inspection of the devicemaker's Cookeville, Tenn., facility, during which investigators found that the company had not validated its sterilization process for its adult or pediatric electrode pads. The facility also did not maintain proper device history records for those devices. The records on file did not include the location of the label and labeling for each product lot or batch, according to the form.

The device history records also did not include full information on examination and release of labeling, including the date and the examiner's signature. The firm also had not established an adequate plan for corrective and preventive actions, instead relying on a document that provided a rough outline for recording CAPA activities.

The company's quality policy and objectives, meanwhile, were not established by management with executive responsibility or available in written form. The quality audit procedures found in the firm's SOPs did not ensure compliance reviews for the quality system, and representatives could not produce any documentation of its management review procedures.

Tyson Bioresearch: Tyson Bioresearch landed a Form 483 from the FDA due to failure to establish adequate procedures for several operations.

A March inspection of Tyson's Miaoli County, Taiwan, facility found the company failed to initiate corrective and preventive actions as required for deviations from its quality objectives in 2015 and 2016. Further, the firm had not validated a process used in production of its glucose test strips.

The firm's handling of complaints also contravened its standard operating procedures. A review of several complaints related to the company's blood glucose monitoring system found none contained documented evidence of an evaluation for medical device reporting.

Lastly, the firm's written procedure for medical device reporting was simply a copy of the FDA's MDR regulation.

OsteoSymbionics: Devicemaker OsteoSymbionics must correct several problems uncovered by FDA investigators, including CAPA procedures and non-conforming materials reports (NCMRs).

The FDA issued the company a Form 483 after a March inspection of its Cleveland facility. The inspection found the firm had not completed a CAPA opened in June 2015. Moreover, according to the form, the company's NCMRs did not clearly document all investigative activities as required by the company's own procedures. Ten of 14 NCMRs reviewed did not document why no investigation was required, and three had no information in the investigation and approval sections.

In addition, the company's supplier files did not comply with the firm's Supplier Evaluation and Selection SOPs, according to investigators, with several missing components such as evaluation records, up-to-date ISO certifications and supplier quality monitoring.

Lastly, according to the FDA, a heat sealer used for sterile packaging of the company's cranial implants was calibrated for time and temperature but not for pressure, with the last calibration occurring nearly two years ago.

Southeastern Technology: Following an FDA inspection, Southeastern Technology faced sanctions for its process control procedures and personnel training.

(See **483s***, Page 6)*

HPRA Issues Guidance On Device Standalone Software

Ireland's Health Products Regulatory Authority released new guidance on medical device standalone software.

The software is considered an active medical device, the guide notes, so it must be assigned one of the HPRA's four risk classifications, I, IIa, IIb or III. The classification determines which conformity assessment procedure the software must undergo.

The process for Class I standalone software, for example, does not require the input of a notified body; all such software may bear the CE mark if the sponsor complies with the European Commission's declaration of conformity procedure. All other standalone software is eligible for the CE mark if it follows the relevant requirements for its classification, according to the guide.

To receive the required CE mark, device sponsors must provide a clear definition of the software's intended use that incorporates all functions. This includes a consideration of whether the software performs an action for the benefit of an individual patient; if its function is for a purpose included in the definition of a medical device; if it is acting as an accessory to a medical device; and if it performs an action on data beyond storage, archival, communication or simple search.

Standalone software manufacturers also must identify the essential requirements that apply to them based on intended purpose. The manufacturers also must document all solutions adopted to prove compliance with the essential requirements. The guide suggests a checklist such as that included in HPRA's guidance on compliance with European Communities regulations.

Manufacturers must consider data protection and security, including minimum hardware requirements, IT networks characteristics and IT security measures, according to the guide.

Read the HPRA guide here: www.fdanews.com/06-28-17-HPRA.pdf. — Zack Budryk

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483s, *from Page 5*

In an April inspection of the firm's Murfreesboro, Tenn., facility, the FDA faulted the devicemaker on its process controls for the cleaning line as identified by its SOPs. Investigators interviewed a cleaning line operator and a regulatory compliance manager and found the facility did not use its conductivity meter to verify cleaning solution concentration, even though the company's cleaning tank solution test log was fully filled out.

The FDA also noted that the facility did not maintain documented personnel training records.

Innovative Sterilization Technologies: Problems with Innovative Sterilization Technologies' CAPA procedures, complaint handling and MDR processes earned the devicemaker a Form 483.

The FDA issued the form following an April/March inspection of the firm's Dayton, Ohio, facility. Investigators noted numerous problems with the facility's CAPA procedures. The company SOPs had no clear definition of "unfavorable trend," and the company failed to initiate a CAPA in response to trends that required one according to the SOPs.

The company's complaint SOP, meanwhile, did not properly define how to document investigations and complaint closures for cases where the device was not returned for evaluation. The company voided nearly 50 complaints because the product was never returned.

The agency also faulted the company on its procedures for validating sampling methods, finding that the SOPs did not define their selection and use. Lastly, the company's written MDR procedure did not include a system to determine when a complaint qualifies for reporting.

The 483s can be read here: www.fdanews.com/06-29-17-Five483s.pdf. — Zack Budryk

MHRA Updates Guidance On UK Notified Bodies

In a decision associated with the United Kingdom's withdrawal from the European Union, the UK's Medicines & Healthcare products Regulatory Agency issued updated guidance with new links to notified bodies permitted to undertake conformity assessments of medical devices in the UK.

Conformity assessments are required before a CE Mark is issued for marketing authorization. The following notified bodies can conduct conformity assessments in the UK:

- Amtac Certification Services;
- BSI Healthcare;
- Lloyd's Register Quality Assurance;
- SGS United Kingdom; and
- UL International (UK).

The MHRA and the European Medicines Agency are very intertwined, so it will be especially difficult for the MHRA to make a clean break, but it's unclear how the UK regulatory system will work within the EU regulatory scheme as the UK government negotiates the terms of its withdrawal from the EU.

BSI said its role as an EU notified body won't change following the UK decision to leave the EU. The standards organization is working closely with the MHRA and the Department of Health to ensure "continuity of our full scope designation" as a notified body for medical devices.

BSI plans to use the existing mechanisms for non-EU member states to fully participate as EU Notified Bodies — and it cites examples of designated organizations in Norway, Switzerland and Australia via mutual recognition agreements, all of whom are recognized as Notified Bodies for the purposes of the EU legislation.

BSI anticipates that the UK will continue to participate in the European standards system post-Brexit.

BSI said it expects to be in the first wave of notified bodies designated under the recently passed EU Medical Device and IVD Regulations, and it is investing heavily to meet the new requirements.

The EU's new Medical Device Regulation has introduced significant compliance headaches for manufacturers — including new harmonized standards, classification rules, and conformity assessment procedures.

Some devices will have to be reclassified under the MDR's new classification rules. There are four device classifications (I, IIa, IIb, and III) and four groups of classification rules encompassing non-invasive devices, invasive devices, active devices, and a catch-all category of special rules.

Each device class has more than one conformity assessment pathway. There are specific requirements for Class III implantable and Class IIb implantable devices, as well as separate requirements for Class I sterile devices, reusable surgical instruments, and devices that have a measuring function (*IDDM*, March 1).

Read the MHRA guidance here: www.fdanews.com/06-28-17-UKbodies.pdf.

BRIEF

Better Use of Existing Data Could Identify Safety Issues Sooner: CHOP Reports

The FDA could more quickly identify medical device safety problems by better analyzing existing administrative data, according to researchers at the University of Michigan's Center for Healthcare Outcomes and Policy.

For example, issues with the Lap-Band gastric device could have been identified earlier by analyzing medical diagnosis codes and claims data going back to 2009, the CHOP researchers report.

Looking at simple measures such as payments for device removals and identifying trends earlier could have saved about $1 billion between 2010 and 2014 on reoperations, they estimate. Regulators projected reoperation rates at 4 percent based on clinical trial data even as claims data put the figure at 50 percent.

APPROVALS

ConforMIS Hip Replacement System Gets 510(k) Clearance

The FDA has granted 510(k) clearance to ConforMIS' iTotal Hip Replacement System.

The devices use single-use 3D-printed instruments in combination with the company's patient-specific technology.

The system uses the personalization technology to design customized knee implants, cutting out risks associated with hip replacements such as dislocation, uneven leg lengths and limited reproducibility. Because the replacement hips offer a better match for the patient's anatomy, the system can address these shortcomings and improve patient outcomes, said Scott Ball, M.D., of the University of California, San Diego's Department of Orthopedic Surgery, a member of the device's design team.

FDA Clears Custom Ultrasonics to Resume Manufacturing Endoscope Reprocessor

The FDA cleared devicemaker Custom Ultrasonics to resume manufacture of its System 83 endoscope washer-disinfector.

The agency had previously required the company to perform validation testing for the device's water filtration system and its inline disc filter. The filters underwent testing by independent laboratories with no change in design, and the agency then accepted the performance data, the company said.

The FDA has reinstated the use of the components in flexible endoscopes that are not duodenoscopes. The company is currently working with the FDA to validate the system for duodenoscopes, and it strongly recommends against reprocessing those until further notice.

LiveNova's Epilepsy Device Gets Expanded Approval for Use With MRIs

The FDA granted an expanded approval for LiveNova's AspireHC and AspireSR vagus nerve stimulation devices to allow use in combination with MRIs.

The devices prevent or shorten seizures in patients with drug-resistant epilepsy by sending mild pulses to the vagus nerve.

Previously, the device could only be used with special MRI equipment. Under the expanded access, the AspireHC and AspireSR models can now be used with any MRI.

Royal Philips Gets FDA Clearance For Latest Radiology Platform

Royal Philips announced FDA marketing clearance for its IntelliSpace Portal 9.0 radiology platform.

The platform uses multimodal applications that allow radiologists to visualize and quantify extremely subtle symptoms and differences over time, according to Mark van Buchem, professor of neuroradiology at the Leiden University Medical Center, one of the platform's development partners.

The platform has been available outside of the United States since last November and is set to hit the U.S. market by the end of June. The newest version will feature additional applications for longitudinal brain imaging, multi-modality tumor tracking and optimized lung nodule assessment.

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Drug or Device? How the 21st Century Cures Act Impacts Combination Products

Combination products remain one of the most difficult regulatory challenges for life sciences innovators.

Which FDA Center has the lead?

Will I need one marketing application or two?

Will I need a drug to be cross-labeled and approved for use with my device?

These and many more questions can make combination product sponsors feel like they are entering an unforgiving regulatory labyrinth.

The 21st Century Cures Act requires the FDA — over the next several years — to issue guidance that will create a structured process and best practices for managing the development and reviews of drug/device/biologic combinations. The law provides for a streamlined approach to GMP for combination products similar to what the agency has recently announced through rule and guidance.

Drug or Device? How the 21st Century Cures Act Impacts Combination Products takes a close look at the FDA's new authority governing combination products, as well as several new provisions under the 21st Century Cures Act that could usher in a new era of interdisciplinary product reviews at the FDA. You will learn:

- How the 21st Century Cures Act defines primary mode of action
- How to use pre-RFD (Request for Designation) meetings with the FDA to hammer out a customized review process that meets the sponsor's needs
- And more...

Order your copy of **Drug or Device? How the 21st Century Cures Act Impacts Combination Products** for practical advice on the newest changes in the law on combination products and a look around the corner at how sponsors of combination products should seek to position their products to ensure a least burdensome and optimal regulatory pathway.

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