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Industry Expects GAO Report To Challenge 510(k) Program

A forthcoming government report examining the FDA's 510(k) program is expected to be critical and will likely re-categorize Class II devices, according to industry experts.

Although the Government Accountability Office's (GAO) findings on the 510(k) process will not be released until later this year, the device industry is confident the report will be negative and will recommend changes, Pat Schrader, Becton Dickinson's senior vice president of Regulatory & External Affairs, said at last week's AdvaMed 2008 Conference.

The FDA has identified more than 2,300 medical devices, from syringes to catheters, as Class II devices. Since Class II constitutes such a broad range of products with differing risk levels, industry

*(See **GAO**, Page 2)*

Senator Takes NIH to Task Over Hiring Ethics

Sen. Chuck Grassley (R-Iowa) says a cardiac expert hired as a contractor by the NIH is still employed by a heart-device company and praised its product in a recent press release.

In a Sept. 23 letter to NIH Director Elias Zerhouni, Grassley questions Marvin Konstam's work for the National Heart, Lung and Blood Institute (NHLBI) and seeks a response by Oct. 7. The senator says he is trying to determine whether the agency is attempting to circumvent conflict-of-interest policies by hiring contractors as medical experts instead of as full-time employees.

Konstam was hired by the NHLBI in January when he was medical director at Orqis Medical, a company that develops devices to treat heart failure, and on staff at the Tufts University School of Medicine and the Tufts-New England Medical Center. According to Grassley's letter, Konstam still holds those positions.

*(See **Conflict**, Page 6)*

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expects the GAO report will recommend dividing the class, Schrader said.

Based on evidence from other regulatory systems that have more than three classes of devices, Class II will likely be split into either two levels, one for low risk and one for high risk, or three levels — low, moderate and high risk.

“Life-supporting devices in Class II are what generally make people like the folks who sit in Congress nervous as to whether there is enough evaluation,” Susan Alpert, Medtronic’s senior vice president and chief quality and regulatory officer, said. Congress also is concerned that the program has not evolved fast enough to keep up with new technologies.

Industry representatives informed Congress and the GAO that the FDA has the ability to make changes, and the program is designed in a fashion that allows gradual evolution. It also was pointed out that there is no data suggesting a significant number of unanticipated or unmanaged risks in the 510(k) program. This is because 510(k)-cleared devices are not the products that usually cause problems or require drastic recalls.

“The reality is that the program has done quite well,” Alpert said. “This doesn’t mean that it can’t be made better.”

Schrader said the program is unique and sometimes misunderstood. She suggested last spring that improvements be made to the 510(k) review process. She told the FDA and Congress that if they better understood the role of design controls, the product-development process would be more appreciated (*D&DL*, March 31).

Because product life cycles are short and new 510(k)s are required for next-generation devices, the program allows for diversity within the industry. In turn, the industry relies on the program to be predictable so it can build upon developed data and accepted test methods and expectations.

“The 510(k) program has the flexibility to ask for what is needed while assuring a reasonable level of safety for public interests,” Schrader said. “And it’s important that FDA has that flexibility, or everything that might need a clinical trial would need a PMA.”

The GAO is briefing Congress on its findings this week and is waiting on the FDA’s comments before releasing its report, according to GAO spokeswoman Marcia Crosse. She anticipates the report will be made public in late November. — Renee Frojo

Medtronic Bids to Take Over CryoCath

Canadian-based CryoCath is recommending that its shareholders accept a takeover bid offered last week by Medtronic.

The Minnesota company made a cash offer of \$8.75 Canadian per share for all outstanding CryoCath shares — a total of \$400 million Canadian (\$380 million U.S.). The offer represents a 97 percent premium to last Wednesday’s closing price of the common shares and a 93 percent premium to the volume-weighted average trading price of the shares for the previous 20 trading days, Medtronic says in a statement.

Information about the terms of the offer will be mailed to CryoCath shareholders and then posted at www.sedar.com. The companies expect the acquisition, which is subject to the tender of at least two-thirds of CryoCath’s outstanding common shares, to be completed later this year.

CryoCath has annual sales of more than \$40 million Canadian for its cryotherapy products to treat cardiac arrhythmias. Arctic Front, its flagship product, is a minimally invasive cryo-balloon catheter designed to treat atrial fibrillation.

“Joining forces with Medtronic at this stage in our development will dramatically expand our reach and accelerate innovation,” Jan Keltjens, president and CEO of CryoCath, says in the statement. — Mari Serebrov

Industry Should Self-Regulate To Increase Transparency

With the credibility of the industry at stake, medical device companies need to proactively approach conflict-of-interest issues to assure lawmakers that transparency is at the forefront of their agendas, industry experts say.

Increased investigation into and growing distrust of industry-physician relationships have led to a nationwide re-examination of such ties. To protect such relationships and avoid further breaches of the public's trust, a panel of experts agreed the industry will need to follow more rigorous, self-imposed compliance programs.

"The environment has changed forever, but the change is one we should embrace," David Dvorak, president and CEO of Zimmer, said at last week's AdvaMed 2008 Conference panel discussion on the issue.

Following the pharmaceutical industry's lead, AdvaMed plans to update its code of ethics to include provisions that would encourage transparency and create a more uniform alliance on the standards governing controversial relationships with physicians and other healthcare providers, according to AdvaMed spokesman Mark Brager.

"We need to make sure that we are filtering any excesses or abuses that may taint the otherwise perfectly bona fide relationships because, at the end of the day, the patients need these relationships to continue to advance the care that they receive," Dvorak said.

The American College of Cardiology (ACC) arranged for professional organizations and industry representatives to meet last month with lawmakers to discuss the Physician Payments Sunshine Act, H.R. 5605, to broaden understanding on both sides of the issue. At the end of that meeting, the only thing lawmakers were demanding was transparency, Jack Lewin, CEO of ACC, said at the panel discussion. However, what the bill asks for is far less than what industry believes is necessary.

Although several industry-recommended changes have been made to the Senate version, S. 2029, AdvaMed said it is concerned that many smaller companies lack the resources to meet the bill's requirements. In a letter to bill sponsors Sens. Chuck Grassley (R-Iowa) and Herb Kohl (D-Wis.), the group said it would continue to seek an alternative approach to exempt companies that make payments to physicians of less than \$250,000 annually (*D&DL*, May 26).

While industry is overall in agreement with the legislation, details have them debating, such as how companies should disclose information and what the exact dollar amount for disclosure should be, Lewin said. For instance, if provisions of H.R. 5605 are not changed, companies will have to publicly display payments for each individual that receives money as opposed to disclosing a total amount.

"Congress doesn't seem to understand that their good intentions end up pushing the partners apart and are preventing us from doing these kinds of things at a time when the government has no resources to help us," Lewin said.

Others on the panel would not be opposed to even extreme measures in the bill. "If everything is disclosed and patients have access to it, the problems that they have can be taken up with their physicians," Ziyad Hijazi, director of the Rush Center for Congenital & Structural Heart Disease, said.

But some think the legislation already has and would further threaten innovation. It is difficult to determine the number of innovators who have shied away from creating new technology because of concerns about conflicting interests, according to John Parrish, executive director for Harvard Medical School's Center for Integration of Medicine and Innovative Technology.

"In my long career-counseling sessions with young physicians, I think yes, we are being hurt

(See [Transparency](#), Page 8)

FDA Approves Boston Scientific's Drug-Eluting Stent

Although it has yet to lift a corporate warning letter for Boston Scientific, the FDA approved a next-generation drug-eluting stent and stent system from the company last week.

Boston Scientific said it will immediately launch its Taxus Express2 Atom paclitaxel-eluting stent for treating small coronary vessels and Taxus Express2 paclitaxel-eluting coronary stent system for treating in-stent restenosis in bare-metal stents.

"We believe this is ... an important indication we have made significant progress toward resolving the issues related to the Corporate Warning Letter," Jim Tobin, president and CEO of Boston Scientific, says in a statement.

Both stents are first-of-a-kind approvals for such devices in the U.S., the company says. The Taxus Express2 Atom is the only drug-eluting stent designed for use in vessels as small as 2.25 mm in diameter. And the Taxus Express2 is the only drug-eluting stent system approved for in-stent restenosis.

FDA Updates Two 510(k) Marketing Guidances

Makers of ultrasound equipment and intravascular (IV) administration sets and accessories now have updated guidance to direct them through the FDA's marketing process.

"Information for Manufacturers Seeking Marketing Clearance of Diagnostic Ultrasound Systems and Transducers," a revision of a 1997 guidance by the same name, tells ultrasound manufacturers they no longer need to submit a 510(k) Special Report if they maintain acoustic output measurements and labeling records for their devices in their device history file. An appendix to the updated guidance suggests ways to document this information.

The new guidance also includes appendices addressing non-original-equipment-manufacturer replacement transducers, reprocessed single-use transducers and recommended labeling for cleaning and disinfecting transducers.

"This is a welcome addition to the range of available drug-eluting stents, since patients with small vessels who are currently treated with bare-metal stents experience high rates of restenosis," Gregg Stone, chairman of the Cardiovascular Research Foundation, says in the company's statement.

Boston Scientific has been waiting for the FDA to lift the 2-year-old warning letter so it can launch the Taxus Liberte in the U.S., which is designed to be a more flexible and deliverable stent than its predecessor, the Taxus Express. The Taxus Liberte is approved in Europe, where it leads the market (*D&DL*, Aug. 25).

Taxus stents are the world's most frequently used drug-eluting stents as roughly 2.6 million have been implanted in patients globally, the company says.

Analysts from RBC Capital Markets predicted last week that Boston Scientific would have trouble selling the "less desirable Taxus stent" (*D&DL*, Sept. 22). — Renee Frojo

The ultrasound guidance supplements other FDA documents regarding the specific content requirements for submitting a premarket notification.

In the revision of its 2005 guidance "Intravascular Administration Sets Premarket Notification Submissions [510(k)]," the FDA advises manufacturers to submit an Abbreviated 510(k) to demonstrate substantial equivalence for a new device. Firms considering modifications to devices they've already cleared should submit a Special 510(k). However, if the company prefers, it may submit a Traditional 510(k) in either case.

The guidance also clarifies the FDA's recommendations for microbial ingress testing for IV devices.

Comments on the guidances may be submitted any time. The ultrasound guidance is available at www.fda.gov/cdrh/ode/guidance/560.pdf. The IV guidance can be found at www.fda.gov/cdrh/ode/guidance/1189.pdf. — Mari Serebrov

FDA: Devicemaker's 510(k) Spinal Screw System Adulterated

Allez Spine's Laguna Pedicle Screw System, a 510(k) spinal fixation system substantially equivalent to Medtronic's CD Horizon spinal system, is adulterated because the firm made significant changes to the device without submitting the requisite premarket notification, according to an FDA warning letter.

The modifications made to the Laguna system — which include technical locking nut changes, treading profile and sterilization parameter changes — could increase the risk of biomechanical failure, and no PMA application or investigational device exemption for the modified device is on file, the Aug. 8 warning letter says.

Allez Spine told *D&DL* that it plans to release a revised design of the Laguna Pedicle Screw System, which would have a new 510(k).

The warning letter, recently posted on the FDA's website, also cites the company for design control procedures, which were not established prior to the first sales of the Laguna system.

A retrospective design plan to implement a design-control procedure was not completed as well, the letter alleges.

No validation or verification procedures were established or implemented for the following design modifications:

- Changing from a welded two-piece lock nut to a one-piece nut;
- Using a conical head on the pedicle screw assembly instead of a spherical tulip head; and
- Making revisions to the tread profile of the locking nut and tulip head.

Although the company told the FDA it has performed retrospective verification and validation on the single piece-locking nut, the change to the conical head and revisions to the latest thread profile, those activities were not

included in the firm's Form 483 response, the letter says.

The warning letter is based on an inspection of the firm's site in Irvine, Calif., conducted in March and April. It also cites the company's operations for the Del Mar Monoaxial Pedicle System.

The company said it takes the warning letter seriously and intends to resolve all issues with the FDA.

CAPAs

Corrective and preventive action (CAPA) activities also are noted in the letter. The company's open CAPAs do not reference all associated complaints and nonconformances, and a CAPA procedure for a two-piece lock nut separation failure was not initiated.

"In the case of the two-piece lock nut failure identified in [a complaint], you identified that a [CAPA] was justified but incorrectly grouped this complaint into a [CAPA] for another issue," the FDA tells the firm.

The agency also notes an incidence in which a CAPA procedure was not verified and validated or appropriate statistical methodology was not used to identify existing and potential causes of quality problems, the letter says.

MDRs

The FDA inspection revealed three product complaints that were reportable under the medical device reporting (MDR) regulation. Those complaints were not reported to the agency in a timely manner, the letter says.

"Each of the three complaints contains information indicating that components of your device failed to seat properly during initial implantation, and that the devices were therefore immediately explanted by the surgeon," the letter says. "Your own analyses detected evidence of cross threading

(See **Allez Spine**, Page 10)

Conflict, from Page 1

Grassley asks Zerhouni for information on why Konstam was hired as a contractor, for details of his NHLBI salary and moving expenses and whether he has received any compensation from other institutions or companies during the time he has been employed by NHLBI.

He also requests copies of Konstam's financial disclosure filings and materials relating to any contract he may have signed with the NIH.

The NIH says it is working with Grassley to resolve his concerns. "To clarify, Dr. Konstam is an employee of Tufts Medical Center. On January 1, 2008, he became an advisor to the NHLBI on an assignment authorized under the Intergovernmental Personnel Act (IPA)," John Burklow, NIH associate director for communications, says in a written response to Grassley's letter.

"Under the terms of the IPA assignment, Dr. Konstam remains an employee of Tufts Medical Center, and he is not authorized to approve or make any grant or contract awards or conduct research in the NHLBI intramural program. The one-year assignment ... is near completion, and Dr. Konstam plans to continue at Tufts Medical Center as Chief Physician Executive of the Cardiovascular Center," Burklow adds.

Tufts Medical Center told *D&DL* that Konstam recently accepted its offer to return to the center at the beginning of 2009 as chief physician executive of its new cardiovascular center after serving a one-year contract as a senior advisor with NHLBI.

In his letter, Grassley discusses the previous case of David Schwartz, who was director of the National Institute of Environmental Health Sciences (NIEHS) from May 22, 2005, to Aug. 19, 2007, but never resigned his position from Duke University.

According to a letter Grassley wrote last year, Schwartz maintained "constant contact" with Duke after taking over leadership of NIEHS.

Grassley reminds Zerhouni of the scandals faced by the NIH in 2003 when financial

arrangements some intramural researchers had with pharmaceutical companies came to light.

During a hearing on the subject in 2004, Grassley says, Zerhouni told Congress, "I have reached the conclusion that drastic changes are needed as a result of an intensive review by NIH of our ethics program, which included internal fact-finding as well as an external review by the Blue Ribbon Panel."

Grassley writes, "While I thank you for the changes that you brought to the NIH, I am concerned that others at your Agency might not share your views. Perhaps others at NIH do not recognize how critical it is to maintain the integrity of the NIH."

Zerhouni, who became the NIH director in May 2002, resigned last week, effective the end of October.

Grassley's letter is available at grassley.senate.gov/news/Article.cfm?customel_dataPageID_1502=17038. — Elizabeth Jones

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FDANEWS

Preemption Ruling Plays Out In Other Device Cases

Since the Supreme Court's February decision in favor of federal preemption in *Riegel v. Medtronic*, device companies have cited it in at least eight court cases, an attorney says.

In some of these cases, plaintiffs' claims that they were entitled to damages under state law for injuries allegedly sustained from medical devices have been dismissed, Stephen Wood of Kelley Drye & Warren said at a recent FDAnews audio-conference. Other cases have been decided for the defendants, and the plaintiffs have appealed.

In *McCutcheon v. Zimmer Holdings Inc.*, for example, the plaintiff filed a common law tort claim, but the U.S. District Court for the Northern District of Illinois found in August that "consistent with *Riegel*, all state common law claims are preempted," Wood said. The case was dismissed with prejudice, and no appeal has been filed.

The court said the plaintiff's claims that the defendant failed to disclose all necessary information to the FDA were preempted by *Buckman v. Plaintiffs' Legal Committee*, an earlier Supreme Court case. The plaintiff's claims that the alleged defects were not discovered until after approval also were preempted, and the court rejected the plaintiff's attempt to cite bills in Congress that would overturn *Riegel v. Medtronic* (*D&DL*, Aug. 11).

In a state case, *Mattingly v. Urologix Inc.*, a Kentucky circuit court ruled in July that the plaintiff's claims were preempted due to failure to establish any unpreempted "parallel" violation of FDA regulations, Wood said. In addition, the plaintiff's claim that Urologix had been negligent in failing to train physicians was preempted since it related directly to the device itself.

The impact of *Riegel v. Medtronic* is limited to devices with a PMA (*D&DL*, Feb. 25). Even then, there are "carve-outs" for cases in which the defendant failed to follow FDA regulations, rendering the device adulterated, and cases in which the defendant granted an express warranty, Wood said.

Moreover, while the decision wipes out a range of claims under state law, it will not end product liability claims. "It's created an incentive for plaintiffs to find evidence that the manufacturer has violated FDA regulations," Wood said.

This has major implications for device companies considering how to apply for FDA approval, he added. The most significant consideration is the design and purpose of the device.

Also, PMA applications can cost hundreds of thousands of dollars while a more limited 510(k) review can cost less than \$10,000.

Since the courts have now drawn a clear distinction between PMA and 510(k) devices, "to the extent the device company has control and there are potentially significant costs of business if tort liability claims are filed in state court, [a devicemaker] might reasonably want to consider a PMA application, if the agency allows it," Wood said. — Martin Gidron

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by the fact that this is a more onerous and more difficult process,” he said.

The panel members agreed that soon everyone will have to follow the same guidelines. But the industry can take a number of steps to lessen the amount of legal restrictions imposed on them.

Foremost, an emphasis must be placed on educating lawmakers and the public on how critical innovation is for patient benefits, the panel said.

Dvorak suggested companies reduce the appearance of conflict by eliminating anything that could be misconstrued by the general public, such as entertainment or big gifts to physicians.

He warned that in the short-term, this could bring some competitive disadvantages if other companies do not follow, but eventually such acts will corrode their collaboration. “We need to prove that we are acting together to be

responsible and that opportunism in this transition period will not be tolerated,” Dvorak said.

Putting funds in the hands of disinterested third parties and allowing them to disseminate the money where appropriate is another way for companies to avoid conflict, he added.

Lastly, companies should separate sales and marketing from the management of their financial relationships. Without appropriate handling of such relationships, Dvorak said, discussion of patient benefit and innovation will be undermined.

“The time to act is now,” he said. “We’re either going to be self-regulated in a responsible fashion through these actions, or third parties are going to intervene and they will draw the lines in a less informed way than what we can do if we step up.”

The Senate bill, S. 2029, can be viewed at thomas.loc.gov/cgi-bin/query/z?c110:S.2029. H.R. 5605 can be seen at www.govtrack.us/congress/billtext.xpd?bill=h110-5605. — Renee Frojo

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FDANEWS

Adopting Monitoring Technologies Is Key to Reducing Costs

Advances in medical device information exchange have created the potential for collaborative data transfer between technicians and physicians to drive product improvement and increase patient monitoring, according to an industry expert.

Such technologies allow physicians to receive real-time diagnostic data. For manufacturers, they have demonstrated improved warranty claim rates, product worth, quality of care and decreased useless spending, Mike Cislo, senior manager of BearingPoint's Life Sciences Supply Chain, told *D&DL*.

Companies such as Medtronic, Boston Scientific and St. Jude have built electronic transmitters into their cardiovascular devices that send updates on a patient's progress to a physician's computer. Potential adverse events can then be spotted before they become life-threatening.

By using different types of wireless telemetry in devices, which send remote measurements and reporting information to a computer system, hospitals can manage where devices are, how many times they have been used and whether they have been calibrated.

These technologies help keep track of patient information, such as when they use a device and what their results were. However, this information exchange raises controversial patient security and privacy concerns, creating a need for systems to depersonalize information.

Until recently, information exchange technology has been seen primarily in higher end devices such as imaging equipment, but lower end device manufacturers are catching on. "If your infusion pumps and heart monitors don't have intelligence and communication technology today, they will in the very near future," Cislo said.

The infusion of this intelligence into lower cost devices will better enable companies to distribute healthcare. It also will open a huge market for device manufacturers, he added.

Some devicemakers say they have struggled to get government and insurers to pay more for the new technology because it is seen as a significant contributor to the rise in overall healthcare costs.

Cislo said payers and providers will come around when they realize the benefits of the technology. Information retrieved from equipment and electronically stored in patient records can provide the basis for reimbursement, he added. — Renee Frojo

| FDA List of Recalls and Field Corrections: Continued from Sept. 17 | | | |
|--|----------------------------|---|---|
| Company | Number | Product | Reason for Recall or Correction |
| Class II | | | |
| Mallinckrodt | 2,546 units | CT9000 injector suspension systems | Tubing metal begins to crack & thin |
| Bard Peripheral Vascular | 12,679 units | Recovery cone removal systems | Potential for handle to detach |
| Teleflex Medical | 14,255 units | Weck, DuraHook; Weck, DermaHook | Bands break within sealed packaging |
| Physio Control | 1,710 units; 1,393 keypads | LifePak 12 defibrillator/monitor; LifePak 20 defibrillator/monitor; keypad replacements | May have a solder defect; thicker keypad may prevent door from fully latching |
| Femo-Washington | 783 units | Model 35A Series mobile transporters | Corner castings on stretchers oversized |
| Biomet Microfixation | 36 units | Stella interdental osteotomes | Working tips thicker than specification |
| Edwards Lifesciences Research Medical | 25 units | Fem-Flex II femoral venous cannula, catheter | Color coded as an arterial cannula |
| Boston Scientific | 20,966 units | LeVeon SuperSlim needle electrodes | Cannula may detach from correct orientation |
| GE Healthcare | 127 units | DST-XL Model 1002375 | Cable failure |
| Medtronic Neuromodulation | 1,500 units | Suction jar lid for Medela Vario 18 vacuum pump | Pumps provided with incorrect suction jar lids |
| Medtronic Neuromodulation | 11,920 units | Synchromed II programmable pumps | Pumps may have been manufactured without propellant |
| AGA Medical | 10 systems; 131 balloons | Amplatzer Delivery System; Amplatzer Sizing Balloon II | Outer pouch seal integrity issue |
| Varian Medical Systems | 241 units | Varis Aria Radiation Oncology Version 8.1 | Dose delivery may be altered |
| Siemens Medical Solutions | 300 units | Update instructions TH003/08/S for SIMIVIEW 3000, SIMIVIEW NT & MEV ASIM S systems | Instruction update for motion-enable switch/holder assembly |
| GE Medical Systems | 720 units | 1.5T & 3.0T Signa HDX MR Systems | Possible misdiagnosis or inappropriate treatment |
| Class III | | | |
| BD Diagnostic Systems/Lee Laboratories | 26 units | FA Streptococcus Group A, 5mL | Incorrect result |
| Siemens Medical Solutions | 539 units | Antares 5.0 ultrasound systems | Software issues may cause distorted images |
| Ev3 | 3 units | IntraCoil self-expanding peripheral stent | Incorrect label |
| Boston Scientific | 80 units | Flexima biliary stent system | Stent may be mislabeled |
| Acumed | 400 screws | Smooth or threaded metallic bone fixation fastener | Product mislabeled |
| Abbott Laboratories | 33,486 kits | AxSYM Rubella IgG reagent pack | Calibration failures due to error codes |

The full enforcement report for Sept. 17 can be seen at www.fda.gov/bbs/topics/ENFORCE/2008/ENF01073.html.

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and other distortions of the components in the returned devices. This information reasonably suggests that your devices malfunctioned, and in a way that could compromise the placement or stability of fixation of your devices.”

The firm’s responses to the MDR citation were deemed inadequate. “You assert that your initial evaluation of the underlying complaints for MDR reportability was correct, based solely on your belief that there was no immediate patient injury reported by complaints, but acknowledge that unspecified information, obtained later in conjunction with other similar complaints, caused re-evaluation of these determinations and subsequent filing of MDRs,” the FDA says.

The agency adds that documentation “did not support the reasonableness” for Allez Spine’s assertion that, upon an initial assessment, the complaints were not reportable as MDRs.

“Even this initial evaluation was not concluded in a time frame that would have supported timely filing if your initial conclusion had been different,” the FDA says.

The warning also cites the firm for failing to have management with executive responsibility ensure that a quality policy is implemented and maintained at all levels of the organization.

The firm’s Form 483 response says its quality system has improved over the past 11 months and meetings are held frequently to make sure it is in compliance with quality system regulations, the letter says.

However, according to the FDA, evidence obtained during the inspection did not support the firm’s claim. “You do not appear to be following your quality manual, for example failing to maintain complete design control records, and to document verification and validation activities,” the agency says.

Allez Spine told *D&DL* it has hired a new CEO who is restructuring the management team to facilitate compliance with the FDA. “The company is in the process of implementing new controls to ensure full compliance,” it said.

The warning letter can be accessed at www.fda.gov/foi/warning_letters/s6925c.pdf.
— Christopher Hollis

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FDAnews

Investigator, IRB in Separate Trials Hit With Warning Letters

The chief of vascular surgery at a university medical center enrolled ineligible subjects in a device clinical trial and did not report unanticipated adverse device effects (UADEs) as required, according to a warning letter recently posted on the FDA's website.

Another warning letter cites an institutional review board (IRB) in a separate device trial for failure to conduct annual reviews of clinical trials it was overseeing.

The posted warning letter to Rodney White at Harbor-University of California, Los Angeles Medical Center does not give details of the trial or the two different exclusion criteria it claims he violated in enrolling the patients. But it says that in doing so, he may have affected "the scientific soundness of the [investigational] plan or the rights, safety or welfare of human subjects."

Enrolling patients who violate exclusion criteria constitutes a protocol deviation that requires the approval of the sponsor, the IRB and the FDA, which White did not obtain, the warning letter says.

UADEs that occur during a clinical trial are to be submitted to the IRB and sponsor as soon as possible and no later than 10 working days after the investigator first learns of them, but White failed to do so, according to the Sept. 5 warning letter, which was based on an inspection conducted May 21 through June 13.

The letter asks White for copies of new policies and procedures that will ensure that only eligible patients are enrolled in his trials and that all UADEs are reported correctly. White did not respond to a request for comment by press time. The warning letter can be viewed at www.fda.gov/foi/warning_letters/s6912c.htm.

A Sept. 2 warning letter to the IRB of Hamilton Medical Center in Dalton, Ga., says that in addition to failing to conduct annual reviews, the board approved studies without a full quorum, lacked written

procedures in certain areas and did not keep adequate documentation.

According to the warning letter, the IRB did not have written procedures for:

- Continuing review;
- Reporting its findings and actions to the institution and the investigator;
- Determining which studies need review more than once a year;
- Determining which studies need verification from sources other than the investigator that no material changes have occurred since the previous IRB review;
- Ensuring prompt reporting to the board of changes in research activities; and
- Ensuring prompt reporting to the board, institutional officials and the FDA of unanticipated problems, noncompliance, and suspension or termination of IRB approval.

Documentation failures include meeting minutes that do not show how members voted, who attended the meeting and whether members with a conflict of interest attended or participated. Some meeting minutes were missing.

Also, the board's membership rosters for several years do not list members' academic degrees, representative capacity and the relationship between each member and the institution, the warning letter, based on an inspection conducted May 20–28, says.

The IRB responded that a new chairman and members have been appointed, that it has registered with the HHS Office for Human Research Protections, that a registered nurse facilitator has been appointed to take meeting minutes and that the board was to meet to develop new policies and procedures. The FDA says this response is inadequate as the board needs to document new or revised policies and procedures related to continuing review.

Hamilton Medical Center did not respond to requests for comment by press time. The warning letter can be viewed at www.fda.gov/foi/warning_letters/s6907c.htm. — Martin Gidron

BRIEFS

FDA Clarifies Status of RF Ablation

The FDA issued a clarification of a public health notification it sent out last December following the reports of death and serious injuries associated with the use of radio-frequency (RF) ablation devices in the treatment of lung tumors.

In last week's clarification, the agency says it has not cleared any RF devices for the specific treatment indication of partial or complete ablation of lung tumors. Thus, manufacturers of RF ablation devices cannot legally market them for this indication until they submit clinical data establishing safety and effectiveness for this purpose.

They also cannot sponsor training for use of their devices for a specific indication that has not been cleared.

However, based on bench-testing data or animal testing, the FDA has cleared such devices for the general indication of soft tissue cutting, coagulation and ablation by thermal coagulation necrosis. "Under this general indication, RF ablation can be used as a tool to ablate tumors, including lung tumors," the FDA says.

The clarification is available at www.fda.gov/cdrh/safety/092408-ablation.html.

Tools to Help With Breast Cancer Tests

A new federal project, funded by the Agency for Healthcare Research and Quality (AHRQ), will develop, implement and evaluate four computer-based decision-support tools to help clinicians and patients better use genetic tests to evaluate and treat breast cancer.

The AHRQ says the first pair of tools will assess whether a woman with a family history of cancer should be tested for BRCA1 and BRCA2 gene mutations.

For women already diagnosed with breast cancer, a second pair of tools will help determine which patients are appropriate for a Gene Expression Profiling test, which can help evaluate the recurrence risk and whether chemotherapy should be used following surgery.

More information about the project is available at effectivehealthcare.ahrq.gov/healthInfo.cfm?infotype=nr&ProcessID=68.

Virtual Colonoscopy Promising

An NIH-funded screening trial comparing virtual colonoscopy, a radiology-based colon screening exam, with more invasive optical colonoscopy revealed promising findings.

Preliminary results of the National CT Colonography Trial in 2,531 participants at 15 U.S. centers yielded a per-patient sensitivity of 90 percent for adenomatous colorectal lesions 1 cm or larger in diameter, a sensitivity comparable with that of optical colonoscopy, the NIH says.

The study results were published in *The New England Journal of Medicine*. Researchers say they hope this technology will encourage more adults to be screened for colon cancer, which affects one in 18 people in the U.S.

More information on the study is available at www.nih.gov/news/health/sep2008/nci-17.htm.

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