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IN THIS ISSUE

Disconnect Between Management, QCU Possible Source of Warning Letters

A recent survey showing that device company executives are often unaware of problems faced by their quality control units may point to an overlooked contributing factor in FDA warning letters, an expert says.

The most common FDA Form 483 observations during the past decade have related to QCU failings, says Crystal Mersh, an executive partner at QxP. To understand why that is, the consulting firm surveyed 400 industry conference-goers about their QCU departments. The results revealed a telling split in understanding of QCU capacity and performance among executives, quality assurance staff and regulatory staff.

For example, executives were far more likely to believe the QCU had adequate resources and sufficient support to fulfill its mission than QA staff, Mersh says.

"Executive management … thinks everything is really OK and good," Mersh told a recent FDAnews webinar. "And the FDA has a bit of a different opinion."

(See **QCU**, *Page 4)*

Saudi FDA Ratchets Up Controls On Device Clinical Trials

Medical devicemakers must now obtain approval from the Saudi Food and Drug Administration before starting clinical investigations in the country, under guidance released May 27.

No investigational device will be cleared from any port of entry before obtaining SFDA approval. However, sponsors may submit a port of entry clearance letter prior to the agency's completion of the review process.

Applicants must provide a signed agreement with the clinical investigation site and the contract research organization, if applicable, an approval letter from the investigation review board, the clinical investigation plan and the investigator brochure.

(See **Saudi Arabia**, *Page 6)*

Power Chair Makers to Pay U.S. $7.5M in False Billing Case

Two power wheelchair manufacturers will pay the U.S. government $7.5 million to settle allegations that they filed false Medicare claims.

The case involves Salt Lake City-based Orbit Medical and its spin-off, Rehab Medical, which were accused of knowingly altering physician prescriptions and supporting data so that power wheelchairs supplied by Orbit would be paid for by Medicare.

Specifically, the government alleged that Orbit sales reps changed or added dates on the records to suggest a physician saw the patient within 45 days of Medicare billing, as is required. The sales reps also allegedly changed prescriptions to make them appear to prove medical necessity and forged physician signatures on prescriptions and chart notes.

The Department of Justice announced the agreements, which include corporate integrity agreements, on May 27.

Orbit CEO Brandon Bliss tells *IDDM* that the 2010 incidents were the work of a few employees at one of Orbit's 26 shops, and came amid a "perfect storm" of lowered reimbursement and increased government scrutiny.

Under the terms of the corporate integrity agreements, both companies must appoint compliance officers and compliance committees within 90 days. Oversight of the compliance committee will fall to the board of directors, which will meet quarterly to discuss the program and report on its progress to the HHS Office of Inspector General. The CIA also requires that all employees receive a written code of conduct requiring compliance with federal rules, as well as a document explaining the policies and procedures of the compliance program.

The CIAs also require the companies to hire third-party auditors to review any claims to Medicare or other government health programs. The OIG will validate the results of the audit.

Bliss says the company has already submitted some of the required compliance plan and foresees no difficulties meeting DOJ's conditions.

The False Claims Act allegations stem from a *qui tam* complaint filed by two former Orbit employees. They will share a whistleblower reward of about $1.5 million.

Orbit and Rehab could not be reached for comment by press time.

View the Orbit Medical CIA at www.fdanews.com/06-08-15-orbit.pdf. The Rehab Medical CIA is at www.fdanews.com/06-08-15-rehab.pdf. — Elizabeth Orr

India Forming Adverse Event Reporting System

India's health ministry will soon roll out a program to collect and monitor adverse events involving medical devices, under the ongoing Pharmacovigilance Programme of India.

In the initial phase of the Materio Vigilance Programme, roughly 20 monitoring centers will be identified, Vivekanandan Kalaiselvan, principal scientific officer with the ministry's Indian Pharmacopoeia Commission, tells *IDDM*.

Rajiv Nath, forum coordinator of the Association of Indian Medical Device Industry, says that a government task force will be formed in July to help shape the plan. While the initiative is much-needed, he stresses that the aim should be to provide trust in the regulatory system and not to scare people away from use of medical technology.

Vijay Venkatraman, managing director and CEO at consulting firm Oviya MedSafe, agrees. Monitoring the benefit-risk profile of medical devices is a step in the right direction toward achieving excellence in the postmarket safety of all medical products in India, he says.

The Central Drugs Standard Control Organization will work with the Sree Chitra Thirunal Institute of Medical Sciences and Technology to design the system. The plan follows a series of high-profile incidents in which faulty products harmed patients (*IDDM*, March 20).
— Jonathon Shacat

Expert Offers Tips on Designing, Conducting Internal Audits

Internal audits can be a great way for a device-maker to uncover quality issues and improve compliance programs, but there are challenges to doing them. The vast majority of manufacturers conduct internal audits soley because the FDA and ISO regulations say they should, says Susan Reilly, owner of the consultancy Reilly & Associates. That results in poorly conducted audits with little or no added value. During a recent FDAnews webinar, Reilly answered questions about how to design and perform effective internal audits.

Question: *Would a company ever need to turn over internal audit reports or findings during an FDA inspection?*

Answer: The regulation does not require that a company present audit reports to the FDA. Obviously, if the agency subpoenas those records, that's a slightly different story. However, FDA investigators can access some audit outputs in the form of nonconformances that have become CAPAs.

Q: *How should you document an internal efficiency audit so the audit report won't pose a burden during regulatory body audits if action is not taken?*

A: Even if you are auditing for efficiency and process improvement, the company will have to defend why it didn't take action. A company could create a separate document that shows it has a process for addressing, handling and presenting to management. Some companies have audit procedures that say all nonconformances require a CAPA. If that is a manufacturer's procedure, then each opportunity for improvement found in the efficiency audit will have to have a CAPA.

Q: *How should a company handle multicultural audit teams or auditors for internal audits, where every team may have different audit etiquette?*

A: All procedures should be written so they can be adjusted depending on how things work where the different organizations are located. What often works well is to assign the lead role to an individual who is from the culture of the facility being audited or who has more experience with that culture, even if this is not the most seasoned auditor of the group. Where there are cultural issues, handling those may be more important than the audit technique and the audit skills for a lead auditor.

Q: *Are there any advantages to doing just a general quality system-based audit versus auditing individual departments?*

A: Absolutely. Often, this is not done because of a resource constraint, but it is always recommended to do both the individual audits and a comprehensive audit. By looking at the whole system, a company can truly see the interactions. Key questions include:

- How is it working together?
- Are we putting emphasis in the wrong areas?
- Is there a gap between this process and that one?

Q: *During the review of audit findings, can the auditor give the auditee advice?*

A: An outside auditor is not going to be responsible for the corrective action or for the re-assessment of that corrective action, so caution is warranted. When dealing with an internal auditor, caution is also recommended because the auditor should not own the corrective response to the finding. There is a risk of the company saying that it did as the auditor suggested, but that action didn't work.

Q: *Are process efficiency findings considered part of preventive actions? If so, do the root cause investigation and corrective actions requirements apply? If not, should a stand-alone procedure be established to document efficiency audit requirements?*

A: If a company has a preventive action process set up, it certainly can use that, but that doesn't always apply if the company is not identifying a trend that has not yet caused a nonconformance. It's more of a "this could be better" analysis. Some companies have processes specifically for program improvements that include a quality plan outlining the actions to be taken, responsibilities assigned and the achievable goals of the plan. This is generally recommended over a preventive action process specifically to avoid the need for a root cause analysis.

QCU, *from Page 1*

That discrepancy can lead to warning letters if executives fail to provide QCUs with needed resources, rendering them unable to properly perform their duties, Mersh says.

Two common trouble spots are lack of technical and leadership skills within QCU and lack of resources. Of those surveyed, 61 percent agreed or strongly agreed that the QCU has the required skills, both technical and leadership, to fulfill its responsibility. While that's encouraging, Mersh says the 28 percent who disagreed and 10 percent who strongly disagreed suggests there is work to be done.

Critical skills for QCU staff include the technical background to understand the company's manufacturing process, strong analytical and reasoning ability and the leadership skills to influence upper management, Mersh tells *IDDM.*

On the issue of resources, respondents varied widely, with 65 percent saying their QCUs didn't have adequate resources and 35 percent saying they did. This could indicate a great deal of variation in how resources are allotted or respondents' opinions as to how resources are appropriate for the QCU, Mersh says.

"In general, the majority of folks agreed that the QCU is not adequately resourced," she says. "And as you can see in the warning letters, FDA is starting to realize this and call this out."

The survey also found some wins for QCU staff. Seventy-nine percent of respondents strongly agreed that the QCU's reporting structure should be isolated to ensure independent decisions. On the other hand, only 39 percent agreed that the decisions of the QCU are fully independent from all company operations.

Seventy-four percent of respondents said that the QCU gets authority and support from executive management. This may indicate that companies are taking note of the FDA's relatively recent attention to executive management on quality system matters and are responding with greater support to their QCUs, Mersh says. — Elizabeth Orr

NICE Issues Guidance on Tests For Cancers, Bacterial Infection

The UK's health care costs regulator is recommending against coverage of two new tests to help diagnose prostate cancer in people who have had a negative or inconclusive prostate biopsy, saying they aren't an efficient use of government funds.

In final guidance issued last week, the National Institute for Health and Care Excellence said that using Hologic GenProbe's Progensa PCA3 and Beckman Coulter's Prostate Health Index to help determine the need for a second biopsy doesn't lead to improvements in the diagnosis of prostate cancer that are large enough or consistent enough to influence current clinical diagnostic practice.

NICE also recommended against Caliber I.D.'s VivaScope 1500 and 3000 systems for diagnosing potentially malignant skin lesions, saying in draft guidance that while they show promise, there is insufficient evidence to recommend their use in routine clinical practice.

In another draft guidance released last week, NICE recommended five procalcitonin assays — Siemens Healthcare Diagnostics' Advia Centaur, Thermo Fisher Scientific's Sensitive Kryptor, DiaSorin's Liaison BRAHMS PCT, bioMerieux's Vidas BRAHMS PCT and Roche Diagnostics' Elecsys BRAHMS PCT — for research use only, pending the outcome of further studies on their effectiveness in clinical practice. The assays measure levels of the biomarker procalcitonin to show whether infections have been caused by bacteria.

Final guidance on the procalcitonin tests and the VivaScope 1500 and 3000 imaging systems is expected in October and November, respectively.

The final guidance on Progensa PCA3 and PHI is available at www.fdanews.com/06-15-NICE-Guidance.pdf.

Comments on the two draft guidances are due June 24. View the drafts at www.fdanews.com/06-15-NICE-Guidance2.pdf and www.fdanews.com/06-15-NICE-Guidance3.pdf. — Jonathon Shacat

Design Control, CAPA Lead To Warning Letter for Nuga

South Korean devicemaker Nuga Medical received an FDA warning letter related to a host of GMP woes, including design control and CAPA procedures.

The Gwangju City company makes therapeutic heating and massage devices.

The Dec. 24 letter says Nuga's design control procedure is inadequate because it doesn't require the company to document investigations into device failures that occurred during design validation. As of the Aug. 25 to 28, 2014, inspection, Nuga hadn't identified design validation failures dating to January 2012.

NUGA's corrective and preventive action policies were also found wanting, with no corrective actions initiated for six of the seven quality issues identified as needing investigation. Further, the company's complaint handling procedures don't include requirements to ensure that complaints are evaluated for reporting to the FDA. None of the 73 complaints Nuga received about heating belts that melted or sparked at the connector was investigated, the FDA says. And the company lacks written procedures for adverse event reporting.

The FDA also dinged Nuga's practices around design changes. For example, the devicemaker failed to document a change in the type of fuse needed for design validation and distributed at least five devices with a redesigned connector without establishing a validation protocol for the change.

The investigator also noted that some checklists for certifying that devices are ready for sale had been marked in advance with how many devices would be rejected after review, and some of Nuga's manufacturing equipment was never qualified per the company's written procedures.

View the warning letter at www.fdanews.com/06-08-15-nuga.pdf. — Elizabeth Orr

Saudi Arabia, *from Page 1*

The guidance also sets out requirements for labeling and progress reports on investigational devices. Labeling must include the manufacturer's name and address, the intended use, the residual risks and a cautionary note.

The label and instructions may be in English if the users are likely to be qualified professionals. Instructions for importers and distributors on handling, storage and transportation, however, should be in both English and Arabic, the guidance says.

The guidance also explains the timeframes in which principal investigators and sponsors must submit progress reports on topic such as adverse effects, plan deviations, recalls, withdrawal of approval and premature termination. Companies should send a clinical trial report to the SFDA and reviewing IRBs within six months of the study's completion or termination.

In the case of emergency deviations, sponsors must notify the SFDA no later than two calendar days after the emergency occurred.

Read the guidance at www.fdanews.com/05-15-SFDA-CIMD.pdf. — Jonathon Shacat

FDA Issues Final Rule On CP Bypass Pumps

The FDA issued a final order reclassifying nonroller-type cardiopulmonary and circulatory bypass blood pumps from Class III to Class II with special controls.

NRP devices for temporary ventricular support will remain in Class III and require PMAs.

The special controls for NPRs cardiopulmonary and circulatory bypass include nonclinical performance testing showing durability, proof of biocompatibility, sterility testing and proper labeling including safety warnings.

The order finalizes a Jan. 7, 2014, proposed order that followed a unanimous advisory panel recommendation in December 2012 for down-classification of non-ventricular support NRPs. The panel based its recommendation on the devices' long history of use in bypass procedures.

Manufacturers of Class III NRP devices have until Sept. 6 to file PMAs. View the June 8 *Federal Register* notice at www.fdanews.com/06-15-bypass-pump.pdf. — John Bechtel

Manufacturers to Add Risks On Labels for Facial Fillers

The FDA is calling for stronger label warnings on facial soft tissue fillers due to the risk of unintentional injection into blood vessels.

The May 28 safety alert warns that the fillers, which are commonly used to lessen the appearance of wrinkles or to make lips and cheeks look fuller, can cause vision problems, stroke or damage to skin and other facial tissue if they are injected into blood vessels.

When this occurs, blood supply to tissue can be restricted or the filler material can travel elsewhere in the body.

The nose, forehead, skin between the eyebrows and nose, and skin around the eyes are especially prone to blood vessel blockage, an FDA literature review shows.

While current labeling on soft tissue fillers mentions the risk of unintentional injection into blood vessels, additional warnings are needed, the agency says. The updated labeling should state that only physicians and others with appropriate training should inject the fillers, and that they should use as little pressure as possible to reduce risk.

Between March 1, 2012, and March 1, 2015, the FDA received 216 adverse event reports related to soft tissue fillers, agency spokesman Eric Pahon says. Of those, 57 described injection into a blood vessel as the cause of the event. Injection into a vessel could not be confirmed in the other 159 reports.

Of the 57 confirmed reports of blood vessel injection, 41 resulted in vision problems, including 32 cases of vision loss or blindness and four cases of stroke.

The remaining 16 involved tissue damage, blockage of blood supply to tissue or whitening of the skin.

The 159 reports of vascular events with unconfirmed injection into a blood vessel included five reports of vision problems, Pahon says. The remaining 154 reports described localized skin reactions, including tissue damage, blockage of blood vessels, whitening of the skin and severe bruising.

According to the American Society of Plastic Surgeons, more than 2.3 million soft tissue filler procedures were performed in 2014.

View the warning at www.fdanews.com/06-08-15-filler.pdf. — Elizabeth Orr

Poor Complaint Handling Lands Insightra Medical a Warning

The FDA slapped a warning letter on a California manufacturer of balloon catheters and inguinal hernia implants for not adequately evaluating complaints.

During a Feb. 19 to 24 inspection of the Insightra Medical's Irvine, Calif., facility, investigators determined that four of 12 complaints were not adequately investigated to determine the cause of device failure. In one case, involving a patient's death, the firm had very limited information on the patient and event, the May 21 letter says. The company conducted an investigation with the device distributor, but the catheter involved in the death was not made available and no further conclusions could be made.

In instances where a distributor doesn't provide information necessary for an investigation, the manufacturer should contact the end user directly, the FDA says. While the user contact information was included in the complaint report, there were no documented attempts to contact the user, the agency adds.

When a device is not returned, companies should test reserve samples or devices manufactured around the same time, review device history records, and analyze any service records or CAPA or nonconforming data related to the device, the FDA says.

View the warning letter at www.fdanews.com/06-15-insightra.pdf. — John Bechtel

BRIEFS

BSX Loses Another Mesh Lawsuit

A Delaware jury ordered Boston Scientific to pay $100 million to a woman who was injured by the company's transvaginal mesh device. The plaintiff, who was implanted with the device in 2009, claims that parts of the product continue to cause pain, despite the fact that she had two surgeries to correct the problem. The jury found the Marlborough, Mass., devicemaker guilty of negligence and failing to warn patients and doctors about possible risks. Last week's verdict is Boston Scientific's biggest payout to date over the devices.

The company announced last month that it would set aside an estimated $119 million to resolve nearly 3,000 cases involving the product. Boston Scientific does not acknowledge any liability or wrongdoing.

Zimmer Divests U.S. Assets

Orthopedics manufacturer Zimmer Holdings has reached agreements with buyers to divest certain U.S. assets, including the Zimmer Unicompartmental high-flex knee system, Biomet Discovery elbow system and Cobalt bone cements portfolios. The move was required by the Federal Trade Commission to secure approval of and address antitrust concerns regarding Zimmer's pending acquisition of Biomet. Zimmer expects to complete the deal in the next few weeks.

The European Commission and Japan Fair Trade Commission have already approved the transaction.

FDA Issues Rule on Male Vibrator

The FDA issued new rules on male vibrators for premature ejaculation, classifying the devices as Class II with special controls. The move comes after British devicemaker Ergon Medical won de novo approval for its Prolong device, prompting the FDA to draw up rules on future, comparable devices. The devices' risks include pain or discomfort, burns, electrical shock, adverse skin reactions, injury caused by device breakage or failure, and interference with other electrical equipment. To mitigate these risks, the FDA is requiring that labeling include specific instructions on proper device placement and use, that the portions of the device that contact the patient be biocompatible and that analysis and testing demonstrate electromagnetic compatibility. The devices are not exempt from 510(k) notification.

Halozyme, Ventana Forge Partnership

Halozyme Therapeutics and Ventana Medical Systems are collaborating on a companion diagnostic assay for use with Halozyme's drug PEGPH20, an FDA- and European Commission-designated orphan drug to treat pancreatic cancer. The assay will be designed to detect high levels of hyaluronan, a chain of natural sugars that can accumulate around cancer cells. Ventana will develop and commercialize the in vitro diagnostic, which will then be submitted for regulatory approval in the U.S., Europe and elsewhere. Halozyme plans a worldwide Phase III clinical study for PEGPH20 in 2016.

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