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Unreported Manufacturing Change Nixes Firm's Preemption Protection

Failure to report a critical change in a Class III medical device can lead to more than a warning letter and other compliance problems with the FDA. One company lost an important protection — preemption of liability when state laws differ from federal requirements.

Advanced Bionics was dealt a blow last month in a product liability case after Judge Barbara Lynn of the U.S. District Court for the Northern District of Texas ruled that the company's preemption defense did not apply because its cochlear implants were allegedly adulterated and therefore not compliant with federal law. The plaintiffs' claims were based on the devices being adulterated.

Scott and Pamela Purcel filed suit against the company and its supplier Astro Seal last year over their son's malfunctioning cochlear implant.

*(See **Preemption**, Page 2)*

GE Healthcare Slapped With Warning Letter Citing CAPAs in IT Division

GE Healthcare's Integrated IT Solutions division allegedly has inadequate corrective and preventive action (CAPA) procedures for its Centricity Imaging and Picture Archiving and Communication Systems (PACS) software packages, according to an FDA warning letter.

The systems are used to access radiology and cardiology images, study worklists, patient folders, diagnostic reports and physician and department information.

The letter, issued Aug. 12 and posted recently to the FDA's website, is the third GE Healthcare has received in the past year and a half (*GMP*, December 2007). The company told *GMP* that the two previous warning letters have been resolved.

*(See **GE**, Page 4)*

Preemption, from Page 1

According to the district court order, the suit centers around a single component of the HiRes90k cochlear implant — a feed-thru manufactured by Astro Seal — that was used to connect the device's internal electrical circuitry to external components.

Advanced Bionics recalled all nonimplanted HiRes90k devices containing Astro Seal feed-thrus in September 2004 because moisture could get into the internal circuitry, which could cause the device to fail.

In July 2003, Advanced Bionics received FDA approval for Pacific Aerospace & Electronics to manufacture the feed-thrus for the implant, the court order says. The company then contracted with Astro Seal to make the component, but the company allegedly failed to notify the FDA of the change.

That failure was cited in an FDA administrative complaint against the company, which was settled for \$1.1 million without Advanced Bionics admitting liability (*GMP*, August). The company president also paid a \$75,000 fine in the settlement.

The Purcels claim the implants were adulterated and violated FDA regulations based on three counts: Astro Seal was not an approved manufacturer of the feed-thrus; Advanced Bionics did not receive PMA for modifications to the feed-thrus; and manufacturing processes did not comply with GMP requirements. The firm was cited in a warning letter concerning the production of the implants in 2005.

Advanced Bionics argued that the claims against it were preempted by the Medical Devices Amendments (MDA) of 1976. The judge disagreed.

“The relevant issue here is whether Plaintiffs' strict liability and implied warranty claims impose duties on medical device manufacturers 'different from, or in addition to' those arising under the MDA, triggering preemption,” Lynn said in her ruling.

Because the son's cochlear implants were allegedly defective and adulterated within the meaning of 21 USC 351, the judge concluded the family's claims are predicated on violations of federal law.

In response to the court order, the company told *GMP* it understood the reason behind the ruling but noted that the plaintiffs' claims are not true. The company also said the allegations stem from the administrative complaint filed by the FDA, adding that the agency could not prove that the firm violated federal law. — Renee Frojo, Christopher Hollis

FDA Approves St. Jude's New Puerto Rico Plant

The FDA granted approval to St. Jude Medical for a new plant in Arecibo, Puerto Rico, for the manufacture of pacemakers, cardiac leads and implantable cardioverter defibrillators (ICDs).

The approval followed a six-month review that included an on-site evaluation by FDA inspectors.

Located in Arecibo's Santana Industrial Park, the 150,000 square-foot facility is comparable to the company's existing manufacturing sites.

St. Jude CEO Daniel Starks has said that moving production operations to Puerto Rico is part of the firm's effort to optimize its tax rate (*GMP*, February). The company declined to comment on its tax strategy.

The new plant coincides with St. Jude's manufacturing facility in Caguas, Puerto Rico, which manufactures more than 220 models of cardiovascular and cardiac rhythm management products and has tripled in size since it began operations in 1987.

Initially, the Arecibo plant will produce pacemakers and leads for domestic and international markets and will begin making ICDs late this year. — Nick Wills

Lack of Quality System Procedures Earns Warning Letter

O’Ryan Industries received a warning letter for allegedly distributing its Endo 150 endoscopic light source and Omega ST sterilizer without having procedures for quality system management or medical device reporting (MDR).

Following an inspection of the firm’s Vancouver, Wash., facility from April 28–30 and May 13 this year, the FDA issued a Form 483 that included 12 violations of quality system regulations and one MDR violation.

The warning letter is dated Aug. 6 and was recently posted to the agency’s website.

The FDA says that the devices do not have PMAs or approved investigational device exemptions. The firm made and distributed the devices without conducting a quality audit since April 1, 2006, according to the letter.

The company also failed to establish procedures for such audits and did not appoint a management representative to ensure that GMP quality system requirements are met and reviewed for their suitability and effectiveness, the FDA says in the letter.

Validation

The company also was cited for “failure to ensure that all inspection, measuring, and test equipment; including mechanical, automated, or electronic inspection and test equipment, is suitable for its intended purposes, and is capable of producing valid results,” according to the letter.

Other quality system violations mentioned in the letter include failure to:

- Establish procedures and document acceptance activities, specifically for the Endo 150 endoscopic light source device;
- Establish complaint procedures and to evaluate complaints to determine if they need to

be reported to the FDA;

- Maintain quality system records; device master records, including specifications for equipment and the production environment; and device history records for each batch, lot or unit;
- Establish control procedures for finished products, including reviews of purchase orders to ensure that “ambiguities and errors” are resolved before distribution; and
- Establish procedures to approve design changes.

The letter also cites the company for “failure to develop, maintain, and implement written MDR procedures” and gives the firm 15 working days to notify the agency of the steps it has taken to correct the violations and prevent them from recurring.

Firm’s Response

O’Ryan President Rick Grant told *GMP* the company “had no idea one particular product — the light source — had a requirement under FDA [jurisdiction].”

The firm intends to move forward and has hired Eisner Safety Consultants to complete all FDA requirements for the product, he said.

The company imports the sterilizer from Apoza Enterprise in Taiwan, which “gave us documents from the FDA that showed the Omega as having 510(k) documentation. But the 510(k) apparently wasn’t finished because the FDA is still seeking information for it,” Grant said.

“We’re using Eisner to respond to the 510(k) requirements,” he continued. “I know the new [510(k)] has been sent to Apoza to resubmit.

“We gave the FDA a time frame by when we would comply and have not heard yea or nay from them.”

The warning letter is available at www.fda.gov/foi/warning_letters/s6895c.pdf. — David Grant

GE, from Page 1

The most recent warning letter says the firm's IT division does not have procedures to evaluate all data sources for CAPAs, such as its complaint-handling system, service data and system performance reports.

"In October 2007, GE Medical Systems in France submitted a correction and removal report for safety issues identified in their Advantage Workstation (AW) product. The evaluation of the same safety issues identified in the GE Healthcare IITS AW Suite version 2.0.1 product (which builds on the AW software code) did not include the consideration that the site in France initially reported these issues," the letter says.

A design change for the AW Suite 2.0.1, originally identified in the AW software code base, was not implemented for the AW Suite 2.0 version, the letter says.

The division's production procedures do not include acceptance activities for CD/DVD burns and electronic distribution downloads to ensure the software matches engineering master files.

Complaint Handling

The FDA also cited the firm's complaint-handling operations. Last November, for example, a customer told the company that CT exam reports were being assigned to incorrect exams. In January, a risk assessment for the complaint classified it as a product safety issue and a work-around was created for the customer.

The company's CAPA review board considered the issue in March and decided that a correction was not necessary.

However, an investigation into the root cause of the problem was not conducted until information regarding the complaint was requested during the FDA inspection, which took place April 15 through May 13 at GE's facility in Barrington, Ill. The letter says a fix for the problem was created in 2005, and a mandatory

safety field modification instruction was created in May.

Complaint-investigation procedures do not include the firm's support central case system in which technicians and engineers document ongoing investigations of service records and complaints, the letter says.

The FDA also has deemed GE's Centricity Imaging devices misbranded because the company failed to submit medical device reports (MDR) within the required 30-day time frame, the letter says.

Investigations

The firm did not document an investigation into a complaint of a patient misdiagnosis that occurred after an incorrect patient file was opened in a PACS workstation. It also did not determine whether it was an MDR event, the letter says.

GE did not submit corrections and removal reports to the FDA within the required 10-day time frame, the letter says.

For example, a correction report was submitted to the agency May 6 for a patient safety issue regarding the wrong study date and time information being displayed in the Centricity PACS software module while a field modification instruction (FMI) development and deployment plan was approved as a mandatory safety FMI last December, the letter says.

The company told *GMP* in a statement that it "takes the warning letter very seriously and is actively working on providing the information requested by FDA in the warning letter and on identifying further enhancements to the site's quality systems that may be appropriate."

Some of the Form 483 observations were resolved before the warning letter was issued, GE said, and the firm plans to respond to the letter this month. It can be accessed at www.fda.gov/foi/warning_letters/s6881c.pdf. — Christopher Hollis

FDA Issues Import Alert For MDR Violations

Swedish firm Cochlear Bone Anchored Solutions has been placed under a U.S. import alert for disagreements with the FDA over the appropriate level of adverse event reporting, according to a recently posted warning letter.

The FDA alleges the company's bone-conducting hearing aids are misbranded because the firm failed or refused to submit complaints within the time frame required under medical device reporting (MDR) regulations.

Cochlear sent the FDA two separate letters in response to violations cited on a Form 483, stating that it disagreed with the agency regarding the "appropriate level of adverse event reporting."

As a result of what it considers an inadequate response, the FDA issued the import alert — or detention without physical examination — on the company's Baha Systems Bone Conducting Hearing Aids, Baha Intenso, Baha Divino and Baha Cordelle II Systems.

An inspection of the firm's Gotebor, Sweden, plant in May 2007 found that the firm's complaint-handling procedure does not detail how MDR events will be investigated and submitted to the FDA within the required 30-day time frame.

The warning letter, issued Feb. 20 and posted recently to the FDA website, says it is unclear how the company will designate problems with the devices as complaints or how it will handle medical problems such as infections within its complaint-management system.

The company also was cited for not providing evidence that the appropriate personnel have been trained to evaluate complaints.

To remove the import hold, the company must provide a written response to the warning letter and correct the violations. The FDA says it will refuse admission of the company's bone-conducting hearing aids until the corrections are made.

The company adequately addressed other GMP violations listed on the Form 483, according to the warning letter. Those violations included:

- Lack of documentation for rework and reevaluation activities of a nonconforming product to ensure it meets current approved specifications;
- Lack of established acceptance criteria prior to the performance of verification activities;
- Incomplete procedures for planning and conducting reviews for design results at all stages;
- Incomplete documentation of employee training; and
- Undated manufacturing records.

The company said in its response it had updated its procedures for verifying device design, the product development process and document control. It also assured that all manufacturing personnel have been retrained in the revised procedures and that this training will be properly documented.

"FDA will ensure, during the next inspection at your facility, that these corrective actions have been properly implemented and maintained," the warning letter says.

Cochlear could not be reached for comment. The letter is available at www.fda.gov/foi/warning_letters/s6884c.pdf. — Renee Frojo

Unreported Changes to Sterilization Wraps Draw FDA Warning

Kimberly-Clark Healthcare failed to obtain marketing clearance before selling 12 models of previously approved sterilization wraps that the FDA considers new products because they were modified with significant changes, a warning letter alleges.

The FDA says the devices are adulterated and misbranded because the company failed to provide adequate justification for not submitting 510(k)s or PMAs for the updated line of sterilization wraps.

In a letter sent to the company last year, the FDA requested clearance numbers, or a basis for

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Revenues at Physio-Control Remain Stable Under Consent Decree

Medtronic booked \$94 million in revenue for its Physio-Control implantable defibrillator business during the firm's fiscal first quarter despite operating under an FDA consent decree.

"We made good progress during the quarter toward resuming full shipments," Medtronic CEO Bill Hawkins said during the company's first-quarter earnings call. "We are working with the FDA to return to full shipments."

Revenue for the division came from sales to critical care customers, governments and markets outside the U.S., Hawkins said. Medtronic's Physio-Control plant is located in Redmond, Wash.

Limited Shipments

The consent decree was approved April 28 by Judge John Coughenour of the U.S. District Court for the Western District of Washington. The decree allows limited shipments of the firm's external defibrillators, including no more than 5,000 new devices for customers to upgrade defibrillators so they comply with 2005 American Heart Association cardiopulmonary resuscitation and emergency care guidelines (*GMP, May*).

Limited shipments of the Lifepak 12, 20 and 1000 external defibrillators to existing Physio-Control customers also are allowed under the decree, as are upgrades to the firm's Lifenet systems.

After saying it intended to spin off the division, Medtronic halted U.S. shipments from the Redmond plant last year for undisclosed GMP deficiencies (*GMP, March*). The firm resumed emergency shipments from the division in mid-2007. After Medtronic temporarily halted shipments from the division, revenues at the unit fell 52 percent to \$69 million.

For the company's 2008 fiscal year that ended April 25, Physio-Control had revenues of \$329 million, including \$101 million during the fourth quarter.

During the recent earnings call, Medtronic's Chief Financial Officer Gary Ellis said the company was making progress with its cost-cutting efforts, which aim to reduce the cost of goods sold by \$1 billion by fiscal 2012. "We are seeing good traction from our design for manufacturing, lean, Sigma and manufacturing consolidation initiatives," he said.

Simplifying product designs, manufacturing more devices in tax-advantaged jurisdictions and implementing lean and Six Sigma production control processes are expected to save the firm \$700 million to \$800 million in recurring savings by fiscal 2012, James Dallas, vice president of quality and operations, told investors at a June analyst meeting (*GMP, June*).

Ellis said the company was becoming more profitable because of the productivity initiative. "We are clearly starting to see some significant benefits of those programs. ... Basically across all of our businesses, we're starting to see improvements in their gross margins," he said. — Christopher Hollis

Firm Cited for Not Revalidating Manufacturing Process

Schroeder Industries' alleged failure to follow quality system requirements during the production of brass rounds used for modulation of beam intensity in radiation therapy earned it a warning letter.

The firm did not validate or revalidate its manufacturing processes after it reported "a loosened bushing on the tooling plate of the milling machine [that] caused a number of the brass rounds to be out-of-tolerance in April," the July 14 letter says.

According to the letter, Schroeder's vice president of manufacturing received a Form 483 listing several GMP violations found during the FDA's May 22 and June 3 inspection.

The agency cited the firm for failing to have written procedures for maintaining patients' programmed files after milling the brass rounds, receiving patient treatment specifications in programmed

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Sterilization, from Page 5

why clearance was unnecessary, for six models of the Kinguard Onestep simultaneous sterilization wrap and the Kinguard sequential sterilization wrap.

Tom Gonzalez, vice president of quality assurance and regulatory affairs at Kimberly-Clark, responded in two separate letters, saying the changes in the models added to the sterilization wrap line between 1991–1995 were not significant enough to require new 510(k)s.

After reviewing the company's response, the FDA determined that significant changes had been made, so marketing these products without approval was a violation. The FDA cites several changes, including:

- Modification of the construction of the Spunguard from two layers to three, which could hinder the ability of the sterilant to penetrate through the wrap to the medical device being sterilized;

- Modification of the Spunguard to a higher tensile strength that may hinder sterilant penetration;
- Lower tensile strength specifications for the current model of the Kinguard, which could weaken wrap strength and lead to package integrity and product sterility issues; and
- A combination of two separate Kinguard and Spunguard models that are manufactured at a higher tensile strength than the previously cleared model.

“These changes to critical attributes of a sterilization wrap, such as construction, weight, and tensile strength, represent significant changes to the device which could affect sterilant penetration ability or maintenance of sterility and, consequently, safety and efficacy of the device,” the warning letter says. “Therefore, clearance of new 510(k)s is required before you may market these devices.”

The June 4 letter was posted recently at www.fda.gov/foi/warning_letters/s6885c.pdf.
— Renee Frojo



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Expert: Lifting of Warning Letter Will Not Help Boston Scientific

Despite expectations that the FDA will lift Boston Scientific's corporate warning letter, which would clear the way for the company to launch Taxus Liberte, its next-generation drug-eluting stent, an analyst says that will not change the firm's competitive position in the stent market.

According to RCB Capital Markets, Abbott's drug-eluting stent Xience, which received FDA approval in July, gained popularity faster than anyone anticipated and now poses the greatest risk to Boston Scientific. It is the only drug-eluting stent to have demonstrated superiority over the Taxus Express stent in two randomized clinical trials.

"It may be a mistake to believe that the U.S. launch of Taxus Liberte will improve [Boston Scientific's] outlook in the [drug-eluting stent] market," analyst Phil Nalbone writes in an analyst note. "We do not believe this second-generation paclitaxel-eluting stent will help [the company] regain any meaningful market share for its Taxus franchise, its most profitable product line."

Two years ago, the firm received the corporate warning letter citing insufficient quality management practices and "serious regulatory problems" at numerous facilities (*GMP*, February 2006).

Lifting of the corporate warning letter will serve "mainly as symbolic event," the analyst says, and changes in the firm's competitive position are not expected.

Since the launch of Xience and Promus, Abbott's private label version of Xience marketed by Boston Scientific, Taxus has lost market, the analyst says.

Taxus Liberte, which is designed to be a more flexible and deliverable stent than its predecessor, Taxus Express, is approved in Europe where it leads the market, Boston Scientific said.

The company has been waiting for the FDA to lift the 31-month-old corporate warning letter before Taxus Liberte can be approved in the U.S.

Resolution of the warning letter has taken more time than executives at the company anticipated, Nalbone writes.

"Efforts to improve the company-wide quality system have required an enormous investment of money and other corporate resources — and we think it's fair to say the entire process has taken far longer than management had imagined when the letter arrived from the FDA more than 31 months ago," the analyst says.

Before the FDA reinspected the firm, it underwent extensive third-party auditing (*GMP*, April 2007).

The company used a centralized audit support system that linked multiple production sites electronically to help manage the third-party inspections process. The goal of the system was to provide sites with consistent, accurate and timely information as well as strategic support (*GMP*, November 2007).

The company has spent millions on its quality systems since the FDA issued the letter (*GMP*, August). Boston Scientific had expected the issues raised in the letter to be resolved during the third quarter, but as of press time, the letter had not been lifted. The FDA reinspected the firm's production operations in February.

Separately, the FDA issued a MedWatch last month for a Class I recall of Boston Scientific's NexStent Monorail, NexStent Carotid Stent and Monorail Delivery System distributed from June 19, 2007, through May 5.

The product was recalled because the tip of the stent delivery system could detach during a carotid artery stenting procedure, leading to increased procedure time, injury to the vessel wall, stroke or emergency surgery to remove the tip. — Renee Frojo, Christopher Hollis

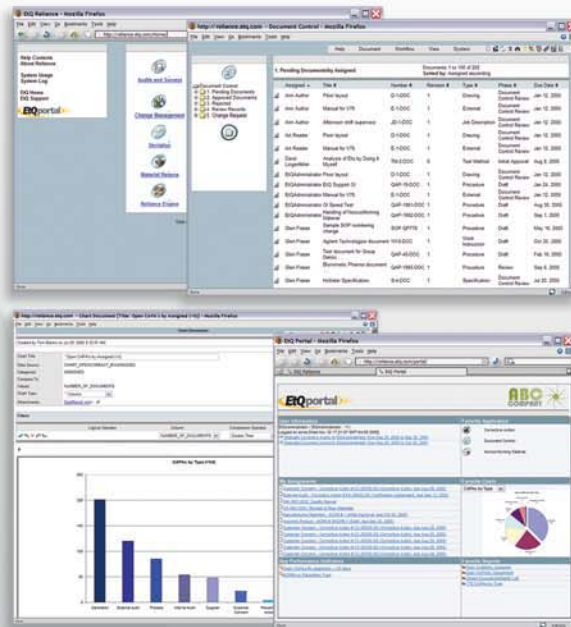
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International Standards for Tubing Misconnections Under Development

An international effort to develop standards that minimize the risk of life-threatening tubing misconnections is gaining momentum, according to an industry group.

An Association for the Advancement of Medical Instrumentation (AAMI) working group and an International Organization for Standardization (ISO) committee are developing international standards to create engineering controls that would make a tubing misconnection physically obvious to healthcare providers who use mismatched tubing sets.

Tubing sets, used to link patients to medical devices or devices to each other, are becoming increasingly prevalent. They can pose serious risks when incorrectly connected to another tubing set or patient access point, Brad Noe, co-chair of the AAMI working group on small bore connectors for liquids and gases in healthcare applications, told *GMP*.

“Theoretically, it [tubing controls] should not allow the connection to occur unless ‘mated’ or matched,” Noe said.

“A clinical area where great strides have been made in this is the practice of anesthesia where certain forcing function standards have been developed so that certain gases are unable to be connected to various connectors, leading to an adverse outcome,” he added.

The U.S. has no standards on how to address issues that may come up with tubing misconnections. There is only a recommendation, administered by the Joint Commission on the Accreditation of Healthcare Organizations, about using oral syringes for administering oral medication. AAMI also has a standard for oral and enteral feeding, but it is voluntary, Noe said.

In Europe, the British National Health Service and the French Ministry of Health are the only organizations beginning to address the issue.

Noe said the target audience for these standards is clinical users, purchasers of tubing sets

and manufacturers. He hopes the market will respond accordingly by changing buying behavior to incorporate the new standards.

The ISO standards will be voluntary. “My perception is that various compliance groups will move this forward,” Noe said.

AAMI says the issue with tubing and catheter misconnections has existed for a long time, but because problems were underreported, it has received little attention. The issue gained prominence only after the Joint Commission published a Sentinel Event Alert in April 2006 that stressed tubing misconnections were a persistent and potentially deadly occurrence.

Since then, the AAMI and ISO committee have been working to develop a foundation document with a flexible standard that would allow for future expansion and revision as necessary. As part of the process, teams are being formed to address specific types and grouping of small bore connection systems, which are the most common way of attaching catheters.

The second draft of the international standard, “Small Bore Connectors for Liquids and Gases in Healthcare Applications — Part 1: General Requirements,” will be ready for review this month. The AAMI plans to publish the final document in January 2010. — Renee Frojo

IVD Classifications Guidance Published by GHTF

The Global Harmonization Task Force’s (GHTF) Study Group 1 has released its final guidance on classification of in vitro diagnostic (IVD) medical devices.

The final version contains some minor additions but no substantive changes from the draft published in May 2007. It recommends a four-tiered, risk-based classification system specific to IVD devices. When more than one classification rule applies to an IVD device, the product is to be classified at the highest risk indicated.

(See **GHTF**, Page 12)

GHTF, from Page 11

Section 6.0, “Recommendations and Factors Influencing IVD Medical Device Classification,” includes two new points concerning stand-alone control materials:

- Stand-alone control materials with quantitative or qualitative assigned values intended for one specific analyte or multiple analytes should be placed in the same class as the IVD reagent(s); and
- Stand-alone control materials with no assigned values intended for use with multiple or single analytes should not be placed in the same class as the IVD reagent(s).

The guidance also expands the types of IVD devices intended for use in blood grouping or tissue typing to ensure the immunological compatibility of blood, blood components, cells, tissues or organs intended for transfusion or transplantation that would fall into Class D, the highest risk.

The list includes ABO system [A (ABO1), B (ABO2), AB (ABO3)], rhesus system [RH1 (D), RH2 (C), RH3 (E), RH4 (c), RH5 (e)], Kell system [Kell (K)], Kidd system [JK1 (Jka), JK2 (Jkb)] and Duffy system [FY1 (Fya), FY2 (Fyb)] determinations. All other IVD devices intended for those uses would be classified as Class C — high individual risk or moderate public health risk.

The two subsets, Class C or D, for blood grouping devices are based on the “nature of the blood group antigen the IVD medical device is designed to detect, and its importance in a transfusion setting,” the guidance says.

Other changes include the addition of prenatal screening tests for congenital disorders and

clarification on how to classify self-administered tests. IVD devices intended for blood gases and blood glucose determinations should be classified as Class C. However, classification of other self-tests is to be determined using a set of seven classification rules provided in the guidance.

IVD devices that are intended as controls — with the user and not the manufacturer setting the qualitative or quantitative value — would be Class B, or moderate risk.

The guidance, “Principles of In Vitro Diagnostic (IVD) Medical Devices Classification,” is available online at www.ghrf.org/documents/sg1/sg1final_n045.pdf. — Meg Bryant

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files, and monitoring and controlling the milling process and device characteristics during production.

The company also failed to ensure that the equipment used to manufacture the brass rounds meets specific design, installation, cleaning and use requirements, the letter says.

The FDA cited the firm for not establishing written procedures for acceptance or rejection of the brass rounds and tooling plates used in production.

Even though the firm’s vice president of manufacturing promised to make corrections, the FDA is requiring a follow-up inspection to ensure the adequacy of any changes, the letter says. A Schroeder spokesman said the firm has sent a letter to the FDA responding to all of the agency’s concerns.

The warning letter is available at www.fda.gov/foi/warning_letters/s6876c.pdf. — Renee Frojo

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Drug ePedigree Bill Stalls, Industry at Odds

New congressional legislation for track-and-trace drug pedigrees is unnecessary and probably will not move out of a House committee in the near future, according to an executive from the National Association of Chain Drug Stores (NACDS).

The Healthcare Distribution Management Association (HDMA), on the other hand, thinks the legislation is needed to safeguard the U.S. healthcare supply chain.

The Safeguarding America's Pharmaceuticals Act of 2008, H.R. 5839, which was introduced earlier this year by Reps. Steve Buyer (R-Ind.) and Jim Matheson (D-Utah), is a bipartisan bill that would establish uniform federal requirements for tracking and tracing prescription drugs from the manufacturer to the distributor and on to the pharmacy (*PIR, May*).

"Part of an overall strategy to help combat criminal counterfeiting, the legislation would strengthen current federal laws and regulations and further secure the nation's prescription medicine supply," HDMA says in a prepared statement.

(See ePedigree, Page 3)

FDA Launches XML Pilot For Clinical Trial Data

The FDA's Center for Drug Evaluation and Research (CDER) is seeking sponsors to participate in a one-year pilot project for electronic submission and processing of clinical trial data in XML format.

The center wants applicants who have submitted files in the Clinical Data Interchange Standards Consortium's study data tabulation model (SDTM) or who are planning to do so within six months.

The SDTM format is detailed in a guidance that tells sponsors how to submit INDs, NDAs and BLAs using electronic common technical document specifications. CDER has been accepting such electronic submissions on a voluntary basis since July 2004.

The pilot project will test data extraction, validation and loading procedures the FDA has developed for Janus, a data repository being developed by the FDA and the National Cancer Institute (NCI) through their Interagency Oncology Task Force.

As part of the task force agreement, the FDA is working with the NCI "to build tools and an environment that facilitates and streamlines electronic interaction and collaboration among FDA and its stakeholders in the regulatory review process," the FDA says. Janus is part of this larger effort to create a common,

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HHS Proposes Updating Code Set, Electronic Transaction Standard

In a move to speed the transition to a national electronic healthcare environment, HHS has proposed regulations to switch to the ICD-10 code set for diagnoses and to adopt the updated X12 standard, Version 5010, for electronic transactions.

“The greatly expanded ICD-10 code sets will enable HHS to fully support quality reporting, pay-for-performance, bio-surveillance, and other critical activities,” HHS Secretary Mike Leavitt says in a statement. “Conversion to ICD-10 is essential to development of a nationwide electronic health information environment, and the updated X12 transaction standards are a critical step in the implementation of these new codes.”

HHS proposes updating the codes providers use to identify specific diagnoses and clinical procedures in claims by Oct. 1, 2011. It wants to switch to Version 5010 for electronic healthcare transactions by April 1, 2010.

Adopted 27 years ago, ICD-9, the current code set, is outdated and has a limited capacity to accommodate new procedures and diagnoses. With only 17,000 codes, it is expected to start running out of available codes next year, HHS says. It also does not have the precision needed for emerging uses such as biosurveillance, and it cannot capture new technology or provide codes for preventive services.

The adoption of the ICD-10 code set, which offers more than 155,000 codes and is used in most developed countries, is expected to:

- Support comprehensive reporting of quality data;
- Ensure more accurate payments for new procedures, fewer rejected claims, improved disease management and harmonization of disease monitoring and reporting worldwide; and
- Allow the U.S. to compare its data with international data to track the incidence and spread of disease and treatment outcomes.

“We recognize that the transition to ICD-10 will require some upfront costs,” Kerry Weems, acting administrator of the Centers for Medicare & Medicaid Services, says in the HHS statement, “but each year of delay would create additional costs, both because of the limitations of ICD-9 and because of the need to employ the greater precision that ICD-10 codes provide.”

HHS is asking for comments on the timeline and the cost-benefit assumptions of the proposed rules. Comments are due by Oct. 21.

The regulations may be accessed at www.cms.hhs.gov/TransactionCodeSetsStands/02_TransactionsandCodeSetsRegulations.asp#TopOfPage. Fact sheets describing the proposals are available at www.cms.hhs.gov/apps/media/fact_sheets.asp. — Mari Serebrov

Expert: Firms Near End of Electronic Transition

The world’s top 20 pharmaceutical companies are completing their transitions from paper case report forms to electronic data capture (EDC) systems for clinical trials, according to an industry leader.

While EDC is still a growth industry, that growth is likely to slow in the next three to five years, Nick Giannasi, senior director of Oracle’s Health Sciences Global Business Unit, told *PIR*.

“One of our clients, a top five pharma with headquarters in Europe, now does 20 percent of its trials on paper and wants to move to all EDC trials within three years,” he said.

“A lot of studies are still run on paper, so I think the EDC market will continue to grow for a number of years and then plateau,” he continued. “Although it will vary slightly in different regions of the world, we expect growth to slow down in the next three to four years and plateau in three to five years.”

One challenge Giannasi cited is “true scalability” of EDC systems so they can easily

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ePedigree, from Page 1

But the legislation probably will not be passed as a stand-alone bill, NACDS predicts. And efforts by Buyer and Matheson to have it attached to the FDA Globalization Act, which is being discussed in draft form, have proven unsuccessful, Paul Kelly, NACDS vice president of government affairs, told *PIR*.

H.R. 5839, which would preempt state drug-pedigree laws and require track-and-trace pedigrees for nearly all medicines, was referred to the House Energy and Commerce Health Subcommittee in April, where no action has been taken.

“Not a whole lot of members in the House have signed on to [H.R. 5839], and there is not a Senate companion,” Kelly said. “I think that’s partly due to our efforts. We let members of the House know when the bill was introduced that it would cause major problems for their neighborhood pharmacies, and I think most members are withholding their support as a result.”

Unlike H.R. 5839, the globalization bill would not require electronic pedigrees or tracking of finished pharmaceuticals, but it does require a pedigree for drug ingredients.

Although Kelly was hesitant to predict whether pedigree legislation would pass after the presidential election, he said it was unlikely that the FDA globalization legislation would move forward early next year without input from the new administration. “A lot will depend on the election and who’s controlling the committees and who’s controlling the White House,” Kelly said. “We will have a new president. That means we will have a new FDA commissioner, and who knows what all that will mean.”

“It seems unlikely that they would move a major food-and-drug bill early next year given that you’re going to have a new administration who’s going to want to have their imprint on anything major like that.”

As for concerns about counterfeiting, Kelly said the drug supply is safe, and there have

not been any major incidents of counterfeiting over the past few years because many states have passed stricter licensing requirements for wholesalers.

Rather than a state-by-state approach, HDMA wants more uniform licensing and pedigree standards, so it “continues to advocate for best practices and utilization of track-and-trace technologies,” the association says, adding that manufacturers, distributors and pharmacies “share a primary responsibility to continuously monitor, protect and enhance” the U.S. healthcare supply chain.

Although NACDS is committed to the security of the supply chain, Kelly said, “electronic pedigree is a solution in search of a problem, and we don’t think it’s worth imposing that kind of cost, with a disruptive mandate on our industry for something that may not be necessary.”

A requirement to implement electronic track-and-trace technology could cost each individual pharmacy store more than \$100,000, he added. According to a written statement from NACDS, that cost is for hardware, software and implementation resource expenses. It does not include costs for building and maintaining data centers to manage the required information.

While manufacturers ship some drugs directly to pharmacies, group purchasing organizations, hospitals, etc., HDMA says distributors handle 80 percent of the prescription medicines shipped in the U.S.

Of that total, distributors send nearly 60 percent to independent pharmacies, food stores, mass merchandisers and chain pharmacies and warehouses. The other 40 percent is distributed to government providers, mail service pharmacies, clinics, nursing homes, hospitals, HMOs and other customers.

A copy of the legislation is available at www.fdanews.com/ext/files/SafeguardingAmericasPharmaceuticalsAct.pdf. — Christopher Hollis, Mari Serebrov

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standards-based electronic infrastructure that supports the submission, validation, data warehousing, access and analysis of clinical and nonclinical study data.

As well as testing the XML format, this phase of the project is meant to:

- Extend the Janus logical data model and service-oriented architecture to support submission of messages in Health Level Seven format rather than the currently used but outdated SAS transport format;
- Integrate Janus with the NCI's Enterprise Vocabulary Service; and
- Test the integration and analysis of clinical study data stored in Janus with pharmacogenomic data received through the Voluntary Genomic Data Submissions (VGDS) program. Potential pilot participants are encouraged but not required to have a VGDS.

This pilot project is the third phase of the implementation of the Janus initiative. Phase 1, a proof-of-concept project, was completed in January 2006. Phase 2 was an operational pilot that integrated two reviewer tools with the repository.

The FDA plans to amend the regulations governing the format of clinical trial and bioequivalence data submitted for NDAs, BLAs and ANDAs in other therapeutic fields and will require all of these to be in a standardized electronic format in the future. The Janus initiative will help pave the way for the transition.

Potential participants in this pilot phase of the project are warned that "our experience during phase

2 has shown that SDTM files routinely fail the Janus validation procedures and cannot be loaded into Janus automatically," the FDA says in a notice. Thus, volunteering companies will have to work closely with Janus technical staff to review the validation errors, correct them and resubmit the files.

Any resulting delays in the pilot "will not impact the regulatory review clock ... or any regulatory actions," the FDA adds.

Companies interested in taking part are asked to submit a written or electronic request to the FDA's Division of Dockets Management by Nov. 17. General comments on Janus are welcome at any time.

The *Federal Register* notice can be read at edocket.access.gpo.gov/2008/E8-19197.htm. More information about the Janus project is available at www.fda.gov/oc/datacouncil/janus_operational_pilot.html. — Martin Gidron

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accommodate additional users. This problem has to be solved on both the front end — the part the user sees on a computer screen — and the back end that programmers are familiar with.

Another problem is lack of interoperability, which can be especially frustrating in the clinical trial arena where sponsors frequently require investigators and sites to use mutually incompatible systems. Giannasi said this problem affects Oracle and fellow industry leaders Phase Forward and Medidata. "Investigators are getting fed up with having to maintain different systems, so there will be consolidations," he predicted. — Martin Gidron

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