FDA Scrutinizing Data Integrity Issues
In Applications: Training Investigators

The FDA is implementing specialized training courses instructing agency inspectors on how to identify data integrity and fraud issues that have surfaced within the last two years, according to Edwin Rivera-Martinez, branch chief for the Manufacturing Assessment and Preapproval Compliance Branch in the Office of Compliance.

“We recognize that this is either a growing problem, or lets just say its a reoccurring problem,” Rivera-Martinez said during the 2007 Parenteral Drug Association (PDA)/FDA Joint Regulatory Conference last month.

“One thing the Center for Drug Evaluation and Research Office of Compliance is trying to do, in conjunction with the Office of Regulatory Affairs, ... is developing specific training courses for our investigators for uncovering … data manipulation” in the preapproval inspections program, Rivera-Martinez said.

(See Data Integrity, Page 2)

EMEA Recommends Viracept Reintroduction; Roche Sees Weak Uptake

The European Medicines Agency (EMEA) recommended the market reintroduction of Roche’s HIV treatment Viracept after the company recalled all batches of the drug due to a manufacturing error, but the firm does not anticipate sales of the product to reach previous levels as patients have since switched to other treatments, Roche told DGR last month.

Viracept (nelfinavir mesylate) had $160 million in sales in 2006, the company said. Roche manufactures the drug for European markets while Pfizer produces the product for the U.S., Canada and Japan.

Roche recalled all Viracept batches earlier this year after a chemical analysis of marketed product revealed the presence of ethyl methanesulphonate (EMS), a carcinogen believed to cause damage to
**Data Integrity, from Page 1**

In 2006, the FDA inspected 10 companies for data integrity issues and found that three were engaged in questionable practices. This year, there were requests to inspect 10 to 12 firms for similar data-related issues, and inspection reports from those audits are just now coming in, Rivera-Martinez said.

Data falsification, which is becoming an increasing focus in the FDA’s preapproval inspections program, has been occurring in GMP operations, contract laboratories, contract manufacturing facilities and clinical investigator sites and the data manipulation is electronic-based, Rivera-Martinez said.

He indicated the agency often gets tipped-off to such infractions via employee complaints: “You won’t believe how many times we get calls on a weekly basis from informants in your companies.” Rivera-Martinez recommended firms institute whistleblower programs so employees have an incentive to report fraud as most whistleblowers will report wrongdoing anyway, either to the FDA or the company. He said many whistleblowers were not just disgruntled employees.

In addition, companies should audit materials suppliers and contract laboratories because some firms fail to conduct such reviews, Rivera-Martinez said. He highlighted a recent inspection of a contract manufacturer that revealed a failure to report results of an out-of-specification (OOS) result for a degradant.

The original OOS result was based on an approved analytical method, yet the contractor substituted the data with a result from an unapproved analytical method, Rivera-Martinez said.

— Christopher Hollis

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**FDA Plans Draft Guidance Reducing Manufacturing Supplements**

The FDA will no longer accept submissions for approximately 50 types of manufacturing supplements, according to a draft guidance the agency plans to release in the next few months, Helen Winkle, director of the Center for Drug Evaluation and Research’s Office of Pharmaceutical Science, said last month.

“We’re getting ready to put out a guidance within the next few months, which will list a number of supplements that we no longer feel like we will require,” Winkle said at the 2007 Parenteral Drug Association/FDA Joint Regulatory Conference in Washington, D.C.

The FDA told DGR that supplements filed when manufacturers change from one reliable raw materials vendor to another would no longer be required. In addition, the guidance will list supplements that are not required by the FDA, yet are still submitted to the agency. One such supplement includes the testing site change submission.

In addition to the new draft guidance in development, the FDA intends to promulgate revisions to 21 CFR 314.70, the regulation covering the types of manufacturing changes firms must receive FDA approval for prior to implementation, Winkle said. She hopes the draft regulation will be released by the end of the year.

“The most significant proposal is to allow for a category of changes that do not need to be reported to the application,” the FDA said. “These would be handled through risk assessments specified within the companies’ internal change control systems.” In connection with the revised rule, the FDA intends to issue a more extensive guidance on change control, which will likely be released before the draft rule is issued, Winkle said.

Changes to manufacturing requirements for biologic drug products are also under consideration at the FDA. Chris Joneckis, senior advisor for chemistry, manufacturing and control issues at the Center for Biologics Evaluation and Research, said during the conference.

“We are internally upgrading and revising, both administratively and scientifically, how we do our assessing of assays for those products that have lot release … and looking at our lot release process.” — Christopher Hollis
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DNA. Product complaints citing a strange odor emanating from the drug triggered the investigation.

After the recall was initiated, the EMEA’s Committee for Medicinal Products for Human Use recommended suspension of Roche’s Viracept marketing authorization. The European Commission subsequently approved the action (DGR, September).

Following the EMEA recommendation, Roche submitted data to the agency for a revalidated manufacturing process.

The root cause of the manufacturing error was related to the cleaning process of a holding tank used in the active pharmaceutical ingredient (API) production process. When the API was removed from the tank, the vessel was then cleaned with ethanol. Some ethanol was left in the vessel, and when new the API was introduced into the tank, a chemical reaction was triggered, creating the impurity, Roche said.

Roche was in supply discussions with Pfizer as it was correcting and revalidating its manufacturing process. However, those discussions have since concluded without an agreement, Roche said.

In response to the Roche recall, the FDA asked Pfizer to implement a new specification to limit the presence of EMS in its batches of Viracept. However, the levels of EMS in Pfizer’s product were substantially lower than that of Roche’s, Pfizer said last month in a Dear Healthcare Professional letter warning physicians about EMS levels in Viracept.

Pfizer will now only release the drug to the market if it meets new interim specifications agreed to by the company and the FDA. The firm is recommending limitations on the use of the product.

The FDA told DGR it would release a guidance document “in the near future” that will address the appropriate levels of EMS in all products. In addition, the guidance will address other types of impurities.

Both Pfizer’s and Roche’s processes for manufacturing Viracept API involve a step where ethanol comes into contact with methane sulfonic acid, allowing EMS to form, Pfizer said. The presence of EMS in Pfizer’s version of Viracept is not related to a cleaning process, the company said.

According to Peter Spargo, former Pfizer director of European chemical R&D, many drugs are produced where an alcohol, such as ethanol, comes into contact with sulfonic acid to crystallize the active substance so it will have better bioavailability and absorption properties. Spargo is the managing director of UK-based consulting firm Scientific Update.

The FDA told DGR that it is currently developing a plan to assess the potential safety issues for all marketed products that may contain sulfonate ester impurities. — Christopher Hollis

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**FDA Issues Guidance for Biologics Using Spore-Producing Organisms**

Biologic drug manufacturers that rely on spore-bearing organisms such as bacteria to make products such as vaccines may do so in either a separate facility or a contained portion of a larger plant, according to a new guidance from the FDA.

Previously, regulations “required that all work with spore-bearing microorganisms (sporeformers) be conducted in an entirely separate building, or in a completely walled-off portion of a multiproduct building,” with equipment permanently assigned to the spore-bearing organisms alone, the guidance notes. This will prevent the hazard posed by some spores that can cause disease.

Due to technical advances, new regulations came into effect June 1, 2004, that “allow greater manufacturing flexibility.” The final guidance details what manufacturers that work with spore-bearing microorganisms are now advised to do.

However, the guidance encourages firms to use alternatives to spore-forming microorganisms. “Such alternatives could include the use of sporulation deficient strains, or recombinant proteins expressed in nonspore-forming microorganisms.”

The guidance can be accessed at www.fda.gov/OHRMS/Dockets/98fr/03n-0528-gdl0002-vol1.pdf. — Martin Gidron
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Biotech QbD Pilot Program
To Start Within Two Months

The FDA’s Office of Biotechnology Products (OBP) plans to commence a quality by design (QbD) pilot program within the next two months, Helen Winkle, director of the Office of Pharmaceutical Science (OPS), said last month at the Parenteral Drug Association’s (PDA)/FDA 2007 Joint Regulatory Conference.

QbD is when drugmakers establish a range of parameters in the manufacturing process known as a design space, where changes within that range would preempt the need for firms to submit postapproval manufacturing supplements.

OBP is the biologics research arm for OPS, under the Center for Drug Evaluation and Research (CDER).

“In this particular pilot, instead of using the original applications, as we’re not used to getting a lot of [biologic license applications], they’re using mainly comparability protocols,” Winkle said. The agency plans to announce the pilot program in a Federal Register notice.

During PDA’s QbD for Biopharmaceuticals conference earlier this year, Barry Cherney, deputy director of OPB’s Division of Therapeutic Proteins, said the pilot program could initially extend review times for QbD applications due to the increased amount of information required for the submissions compared to traditional marketing applications (DGR, June).

The agency’s QbD pilot program for small molecules has been ongoing for over a year. The program has received 11 application review requests from manufacturers. The FDA has reviewed and approved five submissions, Winkle said.

She said the FDA is in the process of implementing postmarket regulatory agreements for companies that have submitted QbD applications.

Regulatory Agreements

The agreements will list specifically what manufacturing supplements would and would not need to be submitted to the agency.

Roger Nosal, a director with Pfizer’s regulatory Chemistry, Manufacturing and Controls (CMC) unit, has called for the FDA to show regulatory flexibility with QbD CMC regulatory agreements (DGR, June).

The decisions on what supplements will be required would be based on risk assessments, Winkle said. The FDA is evaluating ways to extend these regulatory agreements to firms that have not submitted QbD applications, she added.

The Office of Generic Drugs (OGD) has its own manufacturing initiative called question-based review (QbR). Janet Woodcock, the acting director for CDER, said last month during the Generic Pharmaceutical Association’s 2007 Annual Policy Conference that the QbR program has been very successful, with over 90 percent, or 416, of the submitted abbreviated new drug applications (ANDAs) based on QbR.

QbR, which is based on risk assessments, integrates the concepts of QbD into the ANDA review process. Woodcock said the agency wants to move past QbR for generic drugs, establishing design spaces for ANDAs. — Christopher Hollis
CDER Clarifies 170 Percent Increase in Recalls

Recalls for products regulated by the FDA’s Center for Drug Evaluation and Research (CDER) were up 170 percent in fiscal 2007, according to data released by the agency last month.

However, when the recall data are adjusted to account for the incidents leading to specific product corrections, the number of recalls actually declined.

Of the 977 recalls initiated in 2007, 672 resulted from one unidentified repackager, Deborah Autor, director of CDER’s Office of Compliance, said. The result was a massive spike in Class II recalls, with 860 in 2007, compared with 188 during fiscal 2006. In total, there were 361 recalls in 2006.

Class II recalls, which are less serious than Class I recalls, represent a product correction where use of or exposure to the drug may cause temporary or medically reversible adverse health consequences, or where the probability of serious adverse health consequences is remote, the FDA said.

Earlier this year, Omnicare’s former in-house repackaging arm initiated a recall of over 500 million units of various drugs months after it closed that part of its repackaging operation (DGR, June).

Adjusted Recall Data

When the recall data is adjusted to account for multiple recall incidents, there were only 306 recalls in 2007, compared with 338 in 2006. There were 14 recalls categorized as Class I, 189 as Class II and 103 as Class III, according to adjusted 2007 data.

There were also fewer Class I recalls in 2007 when comparing both adjusted and unadjusted data, Autor said.

She made the presentation on the recall data last month at the 2007 Parenteral Drug Association/FDA Joint Regulatory Conference in Washington, D.C.

In speaking about the annual recall data, Autor said the agency is continuing its effort to conduct root cause analyses to figure out how recalls can be minimized. “We will continue to perform those root-cause analyses and develop proactive responses, and we are using recall data as part of our fiscal year 2007 risk-based site selection model for GMP inspections.”

Sawyie Wang, a consumer safety officer with CDER’s Office of Compliance, Division of Compliance Risk Management and Surveillance (DCRMS), detailed the agency’s risk-based inspections program during the conference. Approximately 50 percent of FDA inspections were based on the risk model, the FDA said.

She said the agency categorizes facilities into three tiers, with Tier I facilities representing the highest risk and therefore having the highest priority for an agency inspection.

The Risk Model

The risk model rates facilities by size, frequency of past inspections, number of FDA field action reports and recalls for products originating from facility, the types of products the facility manufactures (e.g., sterile vs. nonsterile), the risk of cross contamination with other drugs and a firm’s difficulty in controlling the manufacturing process, Wang said.

For example, in fiscal 2007, 60 percent of facilities with harder-to-control manufacturing processes were inspected, while 75 percent of facilities that posed a risk of cross contamination were inspected. Almost 80 percent of facilities that had high numbers of recalls were inspected, Wang said.

The duration since a site’s last FDA inspection was apparently the strongest factor in the site selection process, with over 90 percent of facilities that represented a high risk in that area being audited in 2007.

The biggest problem the FDA has in determining which sites to inspect is actually obtaining data on facilities, John Gardner, director of DCRMS, said during the conference. He anticipates that the problem may be alleviated when the agency’s electronic drug listing rule takes effect, hopefully by the end of the 2007, Gardner said. — Christopher Hollis
FDA Cites Chinese API Supplier

The FDA has ordered that active pharmaceutical ingredients (APIs) manufactured at a Kunshan Chemical & Pharmaceutical production facility be denied entry into the U.S., according to a Sept. 6 warning letter. Kunshan is based in China.

The agency cited two of Kunshan’s production facilities — one newer establishment for not documenting method validation to support proposed specifications and one older site for not cleaning and maintaining production equipment in a good state of repair, according to the warning letter, which was posted on the FDA’s website Sept. 20.

Both sites were cited for a “lack of contemporaneous documentation of production steps in batch records, inadequate instructions in batch records and improper completion of production steps,” the FDA said. Inadequate documentation for calibration of laboratory equipment was cited as well, although the agency said its concerns regarding that issue have been addressed.

Kunshan has the following four API drug master files listed with the FDA:

- Antibiotics doxycycline hyclate and doxycycline USP (monohydrate), used to make tablet and capsule formulations, respectively; and
- Two APIs for seizure medication phenytoin, which is the active ingredient in Pfizer’s Dilantin (phenytoin sodium). There are several approved generic versions of the drug.

Connecticut-based chemwerth, a generic API development and supply firm, has an exclusive license to distribute Kunshan’s doxycycline products in the U.S. Chemwerth President Peter Werth told DGR that the company has not imported doxycycline from Kunshan for quite some time and has never imported doxycycline hyclate API produced by the firm, which is a high-volume product compared with the other version.

However, doxycycline hyclate manufactured by Kunshan has entered the country. According to the warning letter, an unidentified product manufactured at Kunshan’s older facility was made for consumption in non-U.S. markets, but FDA records indicate the company has made several shipments to U.S. firms.

Werth identified that product as doxycycline hyclate API. He said large pharmacy compounding operations might be purchasing the API through channels outside of his firm’s control.

The problems at the newer Kunshan facility will likely be resolved by spring 2008, although the older site will not be the focus of Kunshan’s compliance priorities, Werth said. Until the warning letter is resolved, the FDA will not approve any applications listing Kunshan as the API manufacturer.


MedImmune Resolves FluMist Warning Letter

MedImmune said it has resolved the problems the FDA pointed out in a March warning letter concerning the company’s UK manufacturing facility for its influenza vaccine, FluMist.

The warning letter said MedImmune had failed to appropriately investigate excess bioburden levels in bulk lots of FluMist, among other violations of current GMP (DGR, June).

Following the resolution of the warning letter, the FDA approved FluMist for use in children aged 2 through 5. FluMist’s (live influenza virus vaccine) indication was previously limited to patients aged 5 through 49.

Approval of the vaccine has been held up since May. Originally, the FDA’s Vaccines and Related Biological Products Advisory Committee unanimously recommended approval of FluMist for the new patient population.

It will cost $17.95 per treatment course, and the firm estimates 5 million doses have been produced for this season. — Martin Gidron, Christopher Hollis
Lawmakers Debate Import Safety, How to Stop Counterfeit Drugs

The FDA needs to increase inspections and ensure the safety of imported products over their life cycles to prevent counterfeit and substandard drugs from entering the U.S. drug supply chain, witnesses and lawmakers said during a House Subcommittee on Health hearing last month.

Rep. John Dingell (D-Mich.) recently introduced H.R. 3610, the Food and Drug Import Safety Act of 2007, which would create a user fee on imported food and drug shipments, funds from which be used to hire additional inspectors.

The FDA has not yet taken a position on H.R. 3610, but it will probably do so in the coming weeks, Randall Lutter, agency deputy commissioner for policy, said at the hearing. He added that the agency is taking its own steps to enhance imported product safety, such as finding ways to increase information sharing with other governments and holding meetings with Chinese officials.

Lutter told the committee that the agency should be doing more inspections of imported products.

Lack of Oversight

Dingell grilled Lutter on the number of pharmaceutical imports FDA inspectors examine, GMP requirements in foreign inspection facilities and the number of foreign inspections the agency conducts each year.

Between 2,000 and 3,000 pharmaceutical companies are registered with the U.S. and can ship drugs to the country, Lutter confirmed. He said some of the firms importing drugs have not been inspected in eight or 10 years.

The FDA’s underfunded importation safety system is “as full of holes as a block of Swiss cheese,” Dingell said. He said the lack of money and staff was preventing the FDA from doing its job. “The FDA that says it is being leaner and meaner is instead being leaner and weaker,” Dingell said, adding, “I am going to get you folks, whether you like or not, the resources and authorities you need.”

Reps. Henry Waxman (D-Calif.) and Jan Schakowsky (D-Ill.) said they were wary of the user fee H.R. 3610 would add because the agency relies too much on user fees. FDA Assistant Commissioner for Food Protection David Acheson called user fees a double-edged sword, but agreed that resources needed to come from somewhere to begin new programs.

Dingell defended the additional user fee as necessary. “We cannot trust that kind of activity to an agency so poorly funded and so poorly staffed,” he said.

Several lawmakers raised concerns with counterfeit drugs entering the country. Lutter said there is a flood of counterfeit and unapproved foreign drugs coming into the U.S. The FDA’s main strategy has been to communicate risks associated with the products to the public, he added.

Destruction of Counterfeits

Rep. Steve Buyer (R-Ind.) noted that the FDA does not have the ability to destroy drugs it discovers to be counterfeit. Instead, the most common procedure is for the FDA to return packages with suspected counterfeit drugs to the sender. This policy means the government sends bad goods back to “snake oil salesmen,” Buyer said. The FDA is also concerned with the policy, Lutter said.

Agency Commissioner Andrew von Eschenbach said the FDA would delay reforms to its Office of Regulatory Affairs, including the planned closings of some laboratories, until an interagency working group investigating import safety completes its findings (DGR, August).

H.R. 3610 would prevent the HHS secretary from closing or consolidating any of the 13 FDA field laboratories or any of the 20 FDA district offices. More information on H.R. 3610 can be seen at thomas.loc.gov/cgi-bin/bdquery/z?d110: h.r.03610:.

— Emily Ethridge
FDA Inspectors Focus on Personal Responsibility for GMP Violations

Company employees should be aware of the FDA’s focus on determining individuals responsible for GMP violations found during inspections, Parexel Consulting Vice President of Strategic Compliance Services David Chesney said at an FDAnews audioconference.

Recent enforcement actions reflect how the FDA places great importance on individual responsibility for the company’s acts, Chesney said. For example, warning letters are typically addressed to a company’s president and CEO, and criminal prosecutions usually name individuals as well as the corporation, he said.

Because of this focus, agency investigators are trained to look for and develop evidence on which person to charge in a regulatory action that results from an inspection, Chesney said. He added that the Food, Drug and Cosmetic Act is a strict liability statute, which means that the FDA does not have to show a person intended to violate the law in order to charge the company or individual with a violation.

Inspectors look at which employees have the duty and power to detect, prevent and correct the violation, and which had the responsibility to do so, according to Chesney. To document each employee’s responsibilities, duties and power, inspectors may ask questions about an employee’s direct reports, to whom they report and limits on their authority to act without higher approval.

The FDA Investigations Operations Manual instructs investigators to consider questions such as who knew of violative conditions, who should have known of the conditions, who ordered issues to correct the conditions and who approved or denied steps to correct the conditions, Chesney said.

In addition, inspectors look at what other employees say about who is in charge, whose approval is necessary and who overrules whom, he said. Inspectors need to find out what the organization chart says versus what real life in the office is like, and can use the statements as leads and will look for documented evidence to support them.

Observation of how employees work together in the firm during the inspection also helps investigators determine who is responsible, according to Chesney. Investigators will look for employees who issue orders, employees who react to orders, employees who show understanding of the equipment and manufacturing issues, and employees who supervise others.

Employees should avoid misrepresenting the extent of their authority, blaming others and giving the FDA documents that are beyond the scope of its inspection authority, Chesney advised. Employees should also make sure sensitive documents are out of plain sight, he added.

To determine responsibility, investigators can talk to people outside the company, such as contractors, consultants and pest control services, Chesney added. — Emily Ethridge
PDUFA Directs HHS to Develop
Electronic Track-and-Trace Standards

Under legislation President Bush signed into law Sept. 27 reauthorizing the Prescription Drug User Fee Act (PDUFA), HHS is tasked with developing a standard numerical identifier for tracking drugs in the supply chain.

The legislation, known as the FDA Amendments Act of 2007, was passed by the House Sept. 19 and by the Senate Sept. 20. The president signed it into law just days before the Sept. 30 expiration of the previous PDUFA law.

The law gives HHS until March 2010 to develop a standard for numerical identifiers. The identifier would be applied at the point of manufacturing or repackaging, either on the pallet or package level, and should be “sufficient to facilitate the identification, validation, authentication and tracking and tracing of the prescription drug,” according to the law.

In addition, the numerical identifiers should be harmonized with international consensus standards, if practicable, the law says.

Although HHS has 30 months to develop the standard, EPCglobal — a nonprofit that promotes worldwide adoption of electronic product codes — already has ratified its electronic track-and-trace, or epedigree, standards

Adaptive Designs in Oncology
Depend on Electronic Reporting

Adaptive clinical trial designs derive much of the promise they hold for sponsors of oncology trials from real-time reporting and analysis of the data, which can only be accomplished by electronic means, according to an expert speaking at a recent conference sponsored by the Center for Business Intelligence.

Immediate and actionable data constitute the heart of an adaptive trial, Michael Rosenberg, president and CEO of HealthDecisions, said at the conference. His company has conducted adaptive trials for nearly 20 years. “In the traditional trial cycle, there is some delay between when you get the data and when you can access it,” he said. “With adaptive data, you can act as soon as you get the data.”

An important benefit of electronic data gathering and analysis, which is central to an adaptive trial design, is that it enables sponsors to collect metadata, including performance metrics such as the success of individual sites in enrolling patients, Rosenberg said.

Such metadata “will profoundly change how the industry works,” he said. Collection of site enrollment and other information in an adaptive trial makes distributed management possible, meaning that information
The new law requires HHS to consider radio frequency identification technology, nanotechnology, encryption technologies and other track-and-trace authentication technologies in developing its standard for the program.

In addition to considering new technologies to track medicines, HHS must consult manufacturers, distributors and pharmacies. It also should seek input from the Departments of Justice, Homeland Security and Commerce, according to the law.

The Healthcare Distribution Management Association (HDMA), a trade group representing wholesalers, commended the law. “HDMA is … pleased that new authority has been provided to the FDA to establish standards for numerical identifiers that will facilitate the tracking of prescription medicines,” the group said.

The FDA’s regulatory and criminal enforcement resources will be expanded under the new law, which gives the agency the authority not only to fight counterfeit medications but also to interdict subpotent, substandard, adulterated, misbranded or expired drugs, including biologic drug products and active pharmaceutical ingredients originating from local and foreign sources.

“The [HHS] Secretary shall undertake enhanced and joint enforcement activities with other federal and state agencies and establish regional capacities for the validation of prescription drugs and the inspection of the prescription drug supply chain,” the law says.

Last year, the FDA lifted its long-standing stay on the pedigree requirements stipulated in the 1987 version of PDUFA. However, the U.S. District Court for the Eastern District of New York rejected a requirement that secondary wholesalers pass all the FDA-required information on a pedigree document, specifically data tracing the product back to its point of manufacture.

Under the new law, the FDA’s pedigree requirements still do not mandate electronic track-and-trace technologies. In addition, authorized distributors of record, wholesalers that have a written agreement with manufacturers to distribute their drugs, remain exempt from passing a pedigree document.

As the federal government addresses issues related to counterfeit medications, states are instituting their own pedigree requirements, some of which mandate electronic systems. California, for instance, will require firms to deploy epedigree systems to track medications under a new law that is set to take effect in January 2009. However, the California State Board of Pharmacy (CSPB) has the authority to delay implementing it until 2011.

The CSPB recently held an epedigree workgroup meeting to discuss the implementation of the law and listen to presentations from manufacturers on their progress in deploying the technology.

Virginia Herold, director of CSPB, told PIR that manufacturers in general have concerns about being able to fully deploy the technology by 2009. However, Herold said the board is committed to the 2009 implementation timetable.

— Christopher Hollis

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**eRecords: Quality And Integrity Key**

When it comes to records, whether print or electronic, quality and integrity are key issues, former FDA official Stan Woollen said at an Rx-Trials Institute audioconference.

“I think it’s important to remember that the concepts of data quality and integrity that apply to paper records in clinical investigations also apply to electronic records,” Woollen said in discussing the FDA’s revised final guidance “Computerized Systems Used in Clinical Investigations.”

In electronic recordkeeping, the computer system used must be able to maintain the elements of data quality and integrity, he added.

(See eRecords, Page 3)
Woollen used the acronym “ALCOA” to explain what he considers the quality elements of data:

- Attributable;
- Legible;
- Contemporaneous;
- Original; and
- Accurate.

As for integrity, Woollen said data must be what he calls “The Three C’s” — credible, consistent and corroborated.

With quality and integrity in mind, Woolen said that when data are transferred directly into a remote server, a copy of the data should be maintained at another location, and the copies should be made contemporaneously.

Maintaining a credible, contemporaneous backup copy of data is part of a company’s disaster recovery plan. While the FDA does not require companies to have a backup or recovery plan, Woollen said, it does require them to maintain adequate and accurate records.

“If you didn’t have a recovery plan or a disaster plan and your records were lost, the agency could certainly cite you for failing to maintain the required records,” Woollen explained during a question-and-answer time following his presentation, “New Part 11 Guidance for Clinical Trials: What This Means for You.”

“It couldn’t cite you directly for not having a backup plan or a recovery plan,” he added. “But, it would go after citations regarding failure to maintain the records.”

Responding to a question about when electronic recordkeeping systems fall under Part 11, Woollen said it depends on how the systems are used. “[I]f you’re using an electronic system to print out data and you’re relying on that printed data in your submission or your analysis or your reporting, then … those records wouldn’t necessarily come under Part 11,” he said.

FDA Director Emphasizing Electronic CTD Submissions

Pharmaceutical companies should be developing the capabilities to submit common technical document (CTD) applications electronically, Gary Buehler, director of the FDA’s Office of Generic Drugs (OGD), said.

“I can’t stress enough the importance of developing an electronic CTD format for your manufacturing submissions — it’s critically important,” Buehler said at the American Association of Pharmaceutical Scientists’ Pharmaceutical Stability Testing to Support Global Markets workshop.

Although submitting both new drug applications (NDAs) and abbreviated NDAs in CTD format is recommended by the agency, the FDA may start requiring manufacturers to send electronic versions when such applications are submitted, Buehler said.

“[OGD is] in a critical space crunch with respect to our documents. We will receive 900 applications in fiscal year 2007 or somewhere around there. And the 900 applications added to the almost 800 we received last year and the 800 the year before have completely overwhelmed our storage capabilities,” Buehler said.

The FDA issued a draft guidance on submitting applications in CTD format earlier this year. In 2008, the Center for Drug Evaluation and Research will require that electronic applications conform to CTD format. — Christopher Hollis
that used to filter up through a few layers to senior management can now reach the decision-makers directly. As a result, these managers can get a continuous flow of data rather than receiving bulletins only at discrete points in time.

Distributed management enables sponsors to identify issues before they become problems, Rosenberg said. Sponsors can engage in constant fine-tuning of patient enrollment, training and assessing the performance of clinical research associates, which in turn makes it possible to optimize resources, he added.

One example of metadata collection in an adaptive trial that resulted in unexpected side benefits involved a screen failure rate that was appearing among trial sites. “Normally, it wouldn’t have been noticed till the end of the study,” Rosenberg recalled. However, his firm determined the problem was traceable to those sites that had signed on after the trial was under way. Among these sites, the screen failure rate was twice that of the sites that had been with the trial from the beginning. Providing employee training at the late joining sites soon lowered their screen failure rate so it was equal to that of the early starters.

Rosenberg said the required components of an adaptive trial include:

- A timely, continuous source of data and metadata;
- Real-time reporting systems, which depend on modern technologies, such as digital pens that read responses entered on specially designed grid-based case report forms and capture the data directly through an optical sensor;
- Middleware, which he defined as a means of integrating and summarizing data and metadata; and
- Integration with complementary systems.

Rosenberg cautioned that not all technologies are of equal value. He called web-based electronic data capture a dead-end system with no management capabilities. He said such systems are expensive and do not produce much value at the bottom line. — Martin Gidron

Fulcrum Pharma and Lorenz Form Product Development Alliance

Fulcrum Pharma, a drug development and regulatory services company, and Lorenz Life Sciences have formed an alliance to develop products and software for the drug development process, Fulcrum announced.

Lorenz develops and markets software solutions for the life sciences industry that are designed to aid with submission assembly, review, publishing, validation and management for regulated environments, Fulcrum said.

The companies will establish a joint sales and marketing campaign in North America and Europe to provide electronic publishing solutions. The product, Creative eRegulatory Solutions, will provide a cost-effective, tailored approach to meet the increasing demand for regulatory services, the company said. — Jenn Batchelor