

# DRUG GMP REPORT™

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## INSIDE THIS ISSUE

**Warning Letter:** Private label manufacturer cited for inappropriate production changes, says it will work with the FDA on out-of-spec lot .....[Page 3](#)

**Guidance:** FDA advises firms on parametric release requirements for NDA, ANDA and BLA supplements .....[Page 3](#)

**Recall:** Daytrana troubles for Shire continue, Noven says it has found the root cause of the problem and is working to implement corrective actions .....[Page 4](#)

Discovery Labs to submit data on API impurities this month for investigational drug Surfaxin .....[Page 5](#)

Watson recalls fentanyl patch with reservoir design, Mylan benefiting from matrix design.....[Page 9](#)

Cracked vials spurs recall of Procrit lots .....[Page 10](#)

## OGD Offers to Help Firms Comply With Residual Solvents Rule

The Office of Generic Drugs (OGD) has issued a clarification identifying the information that will be considered acceptable for demonstrating compliance with the new U.S. Pharmacopeia (USP) standard for controlling residual solvents.

“After the revised USP Chapter <467> *Residual Solvents* became official July 1, 2008, attempts at implementation of <467> have resulted in variability in the information being submitted to applications, and to uncertainty regarding what information would be considered satisfactory for demonstrating compliance with that chapter,” OGD writes in an update posted on its website last month.

OGD sent letters in May to manufacturers telling them that all generic drugs need to meet the new standard, not just generics manufactured to USP standards (*DGR*, June).

(See **Solvents**, Page 2)

## Sandoz Gets Warning Letter for Generic Toprol XL Production Operations

The FDA is questioning a decision by Novartis subsidiary Sandoz to continue distributing generic versions of Toprol XL after it found the company did not adequately validate its production process.

“We question the continued distribution of this product until better process controls are implemented and process validation is completed,” the FDA tells Sandoz in a warning letter posted on its website last month.

“You originally decided to temporarily suspend distribution of metoprolol 25- and 50-mg tablets [generic Toprol XL] until the available pre-compression and dissolution data was reviewed,” the FDA says in the Aug. 12 letter. “However, you have decided to resume distribution of these products based on your rationale that successful, routine, finished-product testing of manufactured lots is sufficient proof that the product is of acceptable quality.”

(See **Warning Letter**, Page 7)

## Solvents, from Page 1

New applications and pending original applications that do not demonstrate compliance with USP <467> will be considered deficient. Also, all supplements and amendments submitted that require an acceptable drug product specification or certificate of analysis (COA) for approval that do not demonstrate compliance will be considered deficient.

An applicant must verify vendor statements or COA stating that the USP <467> standard has been met — except when “vendor statements to the effect that certain solvents are not used do not require applicant verification. Additionally, statements regarding compliance with USP <467> are assumed to also address solvents that are not designated as being Class 1, 2 or 3,” OGD writes.

Class 1 solvents, products and excipients should not be used in the manufacturing of drug substances because of their toxicity or effect on the environment. Class 2 solvents should be limited in pharmaceutical products because of toxicity. Solvents in Class 3 are considered risky for humans. However, there are no long-term toxicity or carcinogenicity studies for many of the solvents.

### Demonstrate Compliance Before Approval

An applicant’s commitment to meet USP <467> does not demonstrate compliance except when applications are otherwise acceptable for tentative approval. In those cases, applicants must demonstrate compliance before final approval.

In the case of PEPFAR HIV drugs, tentative approval may be granted if there is a commitment to demonstrate compliance within six months. This extension reflects the critical role of these products in treatment of a significant medical emergency.

OGD will consider an application to be complete if it contains the following information for each ingredient used in the formulation:

- Manufacturer’s COA listing all solvents used in the manufacture of the ingredient or a statement that no solvents are used;
- Updated COA for the ingredient, including

solvent identity, acceptance criteria and analytical method (loss on drying would be acceptable if only a Class 3 solvent is used in the manufacture of an ingredient);

- Test data for solvents, including data for Class 3 solvents;
- Method verification data for USP method and method validation data if non-USP methods are used;
- Demonstration that the ingredient meets <467> option 1 or option 2;
- An updated finished product specification stating compliance (including the option used); and
- Suitable qualification information to support residual solvents that are not defined as being Class 1, 2 or 3 solvents and are present at exposure levels greater than 1.5 micrograms per day.

For nonfunctional coating materials, colorants and flavors, testing of residual solvents present in any ingredient of the component is not necessary.

### Draft Guidance

Pending ANDAs must be amended to include changes required by the new standard “as soon as possible,” the FDA says in a draft guidance released last month.

Drugmakers who hold NDAs or ANDAs for compendial drug products must report changes in chemistry, manufacturing and controls specifications to the FDA to comply with the new standard, the draft says.

The draft adds that the FDA will accept analytical procedures that are not explicitly mentioned for these tests in the revised USP chapter, as long as the procedures are properly described, validated and their suitability verified under conditions of use as described in GMP regulations.

In most cases, drugmakers may submit an annual report to cover changes to comply with the USP standards such as adding a test to a finished

(See **Solvents**, Page 4)

## Private Label Manufacturer Cited For Production Changes

G&W Laboratories scaled up production of its Formulation R hemorrhoid ointment without studying manufacturing changes that could have affected product quality, according to an FDA warning letter.

“This lack of attention to process design appears to have been a factor in inadequate mixing of at least one batch of Formulation R product,” the July 24 warning letter says. Formulation R is an OTC ointment comparable to Wyeth’s Preparation H.

G&W, a private label manufacturer specializing in suppositories, creams and ointments, also was cited for releasing one lot of Formulation R without demonstrating that it met relevant quality control criteria.

Potency specifications for the ointment allow it to be manufactured within a range of 90 percent to 110 percent, and a sample from the lot exceeded the upper limit of the specification, Ronald Greenblatt, president of G&W, told *DGR*.

There was a problem with the homogenizer mixer, which blends ingredients, he said. This critical production step was not adequately controlled, according to the FDA’s letter, but the problem has been fixed, and three lots of Formulation R have since been manufactured successfully, Greenblatt added.

Before the finished product containers were filled, tests on samples located at the bottom of a holding tank revealed that the ointment’s specifications exceeded in-process acceptance criteria, the warning letter says, adding that the lot was not rejected and there was no follow-up to address inadequate mixing.

The FDA also criticized production equipment being used for the company’s hydrocortisone acetate suppositories. “During the inspection our investigators observed multiple conditions of disrepair,” the letter says.

The agency cites deteriorating equipment, including “tape flaking off filling equipment directly

(See **Production**, Page 8)

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## Draft Guidance Details Parametric Release Requirements

Applicants submitting an NDA, ANDA, BLA or supplements to support parametric release for products terminally sterilized by moist heat should demonstrate the reliability of their sterilization cycle, microbiological controls, and monitoring and control of production cycle parameters, the FDA advises in a new guidance.

In many cases, drugmakers fulfill the FDA’s sterility requirements by testing finished units drawn from a given batch. Manufacturers use parametric release — a sterility-assurance release program that demonstrates control of the sterilization process — so they can use defined critical process controls as proof of sterility instead of an actual test, according to the guidance released last month.

“The approval of parametric release practices is based on an assessment of the applicant’s proposed critical process parameters and how they are controlled,” the agency says. “As always, adherence to cGMPs is required for marketed products.”

The terminal sterilization process the company proposes should be the same as what the FDA approved in the product application and should be validated according to the agency’s previous guidance, “Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug product,” which is available at [www.fda.gov/cder/guidance/cmc2.pdf](http://www.fda.gov/cder/guidance/cmc2.pdf).

The FDA says its approval of proposed parametric release programs will be based on how well an applicant addresses the risks to product sterility. The draft recommends applicants indicate how their risk assessment includes current control strategies for the terminal sterilization cycle, assess the risk that these strategies might fail to assure sterility and explain how they have taken prior manufacturing experience and knowledge into account.

Comments on the guidance are due Oct. 6. It can be accessed at [www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2008-D-0391-gdl.pdf](http://www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2008-D-0391-gdl.pdf).

— Martin Gidron

## Daytrana Patches for ADHD Recalled Again

Shire is recalling more of its Daytrana patches for attention deficit hyperactivity disorder, possibly leading to the return of as many as 469,000 patches.

Daytrana (methylphenidate transdermal system) is manufactured by Shire's partner Noven. Earlier this year, Noven received a warning letter from the FDA citing manufacturing problems for the product (*DGR*, February). Shire recently recalled 344,000 patches due to the same problem — user difficulty in removing the release liner from the patch (*DGR*, July).

Shire told *DGR* the firms were getting close to implementing a long-term corrective action for the problem. The company estimates that this latest recall could cost anywhere from \$1 million to \$7 million, depending on how many patches actually are returned.

Many of the patches may not be returned because removing the Daytrana release liner is not always a problem, Shire told *DGR*. The recall concerns patches that are malfunctioning.

The companies have not determined whether temperature or the length of time the product is on the shelf plays a role in the problem. The most recent recall was for lots that were made six to nine months ago, Shire told *DGR*.

“We have identified what we believe is the definitive root cause and are aggressively testing potential solutions that we expect will address the issue,” Noven CEO Peter Brandt says in a written statement regarding the recall.

“Until testing is completed and solutions are implemented, voluntary actions like [this] two-lot recall are possible as we work to assure that patients and caregivers can use Daytrana with the convenience they expect,” he adds.

Although Noven would not give details of the root cause of the problem, it told *DGR* that

the solutions involve changes in the manufacturing process, not to the product's formulation.

Noven also told *DGR* that the FDA has not returned for another inspection of its facility after the warning letter. According to an SEC filing, the FDA Florida district office indicated in March that the firm's response to the warning letter appeared to be adequate and the matter has been referred to CDER for further review. — Christopher Hollis

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### Solvents, from Page 2

product specification or an alternative analytical procedure to a specification. Summaries of data from technical studies and tests are acceptable, but the full documented data should be maintained at the manufacturing site for the FDA to review upon request during a site inspection, the draft says.

The draft guidance also touches briefly on how manufacturers of OTC products subject to monographs can comply with the new standard.

The draft can be viewed at [www.fda.gov/OH/RMS/DOCKETS/98fr/FDA-2008-D-0413-gdl.pdf](http://www.fda.gov/OH/RMS/DOCKETS/98fr/FDA-2008-D-0413-gdl.pdf). Comments are due Oct. 6. — Elizabeth Jones, Martin Gidron

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## Discovery Plans Complete Response For Surfaxin This Month

Discovery Laboratories is planning to submit its complete response to the FDA's third Surfaxin approvable letter in September. The synthetic surfactant-replacement therapy is awaiting approval for the prevention of respiratory distress syndrome (RDS) in premature infants.

The company expects the information to be designated as a Class 1 resubmission, which would be reviewed within 60 days. If approved, Surfaxin (lucinactant) would compete with Abbott Laboratories' market-leading surfactant Survanta (beractant), which is derived from cows and is a \$100 million product in the U.S., according to Discovery.

Surfaxin's development has been plagued by manufacturing issues (*DGR*, September 2007). Shortly after the FDA issued the second approvable letter for the drug in 2006, the company said Surfaxin (lucinactant) process validation batches failed stability tests. The letter requested additional information regarding the tightening of active pharmaceutical ingredient (API) and drug product specifications.

Many of the manufacturing issues the FDA had with the application have been resolved, and the company's production operations passed a preapproval inspection.

The third approvable letter, which was issued after the successful inspection, cited documentation issues and requested the firm tighten specifications for which additional tests were not required, according to the company. However, the FDA requested tests to resolve two other issues.

Several years ago, the company developed a biological activity test for Surfaxin release and stability. Results from that test — when considered with results from an RDS animal model test conducted in 2007 — were used to support the comparability between the drug used during

clinical trials and the product manufactured on a commercial scale.

In June, the FDA requested another biological activity test at a different dosage strength. The company also is conducting a related RDS pre-clinical study in conjunction with the new biological activity test. The tests are ongoing, but the company expects to submit data from them as part of its complete response this month.

"Data from these additional studies will be used to determine the final acceptance criteria for the biological activity test and to further confirm the comparability of Surfaxin drug product used in Discovery Labs' Phase III clinical trials to the commercial manufacturing process for Surfaxin," the company said.

### API Impurities

The FDA also questioned product specifications for lipid-related impurities in Surfaxin's active ingredients, the company said.

The drug has four active ingredients — a novel peptide, a fatty acid and two phospholipids, the company says in a statement. The FDA wants Discovery to satisfy International Conference for Harmonisation (ICH) guidelines for lipid-related impurities for the two phospholipids.

"Discovery Labs has consulted with lipid experts and has been working closely with its phospholipid suppliers to reduce lipid-related impurity levels to the ICH threshold limit," the company says.

Based on recent analysis, the company thinks it can meet the ICH specification. Discovery and its suppliers will be completing the process and generating the necessary data in time for the September submission.

"If Discovery Labs' understanding of the timeline is correct, the potential approval of Surfaxin is anticipated in 2008," the firm says.  
— Christopher Hollis

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## Warning Letter, from Page 1

The company manufactures metoprolol succinate at its facility in Wilson, N.C. The warning letter resulted from inspection findings in March.

Sandoz continues to collaborate with the FDA to promptly resolve the agency's concerns and says all products released and distributed met all specifications, according to a written statement about the warning letter.

Par Pharmaceutical distributes the authorized generic of Toprol XL (metoprolol succinate), which is manufactured by AstraZeneca. Sandoz and KV Pharmaceutical market the two other generics. The drug is a beta blocker indicated to treat hypertension, angina and heart failure. It was a blockbuster medication before it went generic and still has a sizable market.

According to the letter, there were failures in process validation studies for the 50-mg dose of the drug. One validation lot failed content uniformity at high-speed compression while another failed dissolution at high hardness for the four-hour time point.

In response to the process validation failures, Sandoz obtained additional samples from other commercial lots unrelated to the validation study, using one conforming validation lot and two unrelated commercial lots to deem the process acceptable, the FDA says.

"It is not acceptable to disregard the findings in one of the lots by stating that another lot made under the same process had sample results that met the criteria. To the contrary, this is an indication that you have not identified, and are unable to control, those factors that cause variability in the process," the FDA letter says. "This also indicates that you lack a robust process design.

"Consequently, you do not have a high level of assurance that the process is in a state of control and is capable of consistently producing a product that meets specifications," the letter says.

The issues affecting the firm's validation of the metoprolol manufacturing process are a potential indicator of problems with other Sandoz drugs, the letter says.

"We are ... concerned that you may not be utilizing a global approach to the implementation of manufacturing controls. For example, one proposed corrective action at the Wilson site is to implement an automated investigation management tracking system (Trackwise), which is already in use at other Sandoz sites.

"It is our expectation that all Sandoz sites intended to be used for the manufacture of drugs have a comprehensive evaluation to assure compliance with all laws and regulations governing the manufacture of drugs. We request that you provide documentation describing the specific steps you will take to perform these evaluations and to implement the necessary corrective actions at all Sandoz sites," the FDA tells the company.

### Failure to Investigate

The company was cited for failing to investigate or complete reviews on time of multiple products made at the Wilson site.

Sandoz's policy is to complete investigations into failures within 30 days and requires a report for any delays in that process. However, numerous investigations were not initiated or completed until the FDA started its inspection, and the reports explaining investigation delays were not on file, the letter says.

Investigations for 18 rejected lots of generic Toprol XL were not conducted, the letter says. They were initiated after the FDA inspection.

Other investigations — including one for failing dissolution results for the muscle relaxant orphenadrine citrate — were not completed until one year after the failures.

(See **Warning Letter**, Page 10)

## Production, from Page 3

above an uncovered hopper containing product to be filled.” Also, an FDA inspector observed a leaking gasket in the product-transfer line during filling of the suppositories, as well as two leaks in G&W’s purified water system, the letter says.

### Black Particles

The company allegedly failed to conduct a thorough investigation into black particles found in a rejected lot of Formulation R suppositories.

The company’s investigation noted that an unidentified pump was replaced during production of the rejected lot, but the batch record did not document any equipment replacement, the letter says.

The FDA also wanted further analysis of the samples from the rejected lot. The company said the cause of the black particles was clear and further analysis was not necessary, according to the letter.

“We disagree that further sample analysis was not necessary as testing the sample would have provided conclusive results of the black

particles found in the batch,” the FDA says in the letter. “In addition, the investigation also noted the shift mechanic who incorrectly assembled the sine pump was a new employee; however, there was no indication that an assessment was conducted to determine whether other batches may have been impacted and investigated.”

During regular production operations, a sample from the company’s purified water system tested positive for E. coli. However, it was determined that the sample was contaminated during testing by an analyst who had not been completely trained.

Training was completed after the incident, the letter says. However, G&W did not tell the FDA how it would make sure that untrained employees do not perform tasks in laboratory and manufacturing areas of the facility.

Greenblatt told *DGR* his firm is ready for a reinspection and has looked at its production operations from a “systemwide” perspective, not just focusing on the individual FDA observations.

The letter, which was recently posted on the FDA’s website, can be accessed at [www.fda.gov/foi/warning\\_letters/s6874c.pdf](http://www.fda.gov/foi/warning_letters/s6874c.pdf). — Christopher Hollis

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**FDANEWS**

## Watson Recalls Fentanyl Patch With Reservoir Design

Watson Pharmaceuticals has recalled one lot of its 75-mcg/hour fentanyl transdermal system in the U.S. because a small number of patches were leaking the pain medicine.

The recalled patches are from lot No. 92461850 with an Aug. 31, 2009, expiration date. They were shipped between Jan. 30 and March 19. No other strengths or lots were affected, and the company does not anticipate any product shortages as a result of the recall, according to its statement.

Accidental exposure to fentanyl gel may lead to serious adverse events, including respiratory depression and possibly fatal overdose. No injuries have been reported, Watson said.

The fentanyl system is the generic equivalent of Duragesic, which uses a reservoir design and is indicated to manage moderate-to-severe chronic pain. Alza, a Johnson & Johnson subsidiary, manufactures the brand product.

Fentanyl patches have a history of recalls (*DGR, March*). PriCara in the U.S. and Janssen-Ortho in Canada voluntarily recalled all lots of their 25-mcg/hour Duragesic transdermal patches manufactured by Alza because of concerns that the patches might have a cut along one side of the drug reservoir, allowing the fentanyl gel to leak into the packaging. That recall involved patches with expiration dates on or before December 2009.

The PriCara and Janssen recall also affected the 25-mcg/hour authorized generic version of the product marketed by Sandoz in the U.S. and by Ranbaxy Laboratories in Canada.

After the Duragesic recall, Actavis announced a voluntary recall of 14 lots of its generic fentanyl transdermal product sold in the U.S. as a precaution. The recall was expanded later to include all lots.

The Actavis recall included patches manufactured by Corium International and sold in the U.S. That product may have had a fold-over defect that could cause the patch to leak fentanyl gel, but the company said it was unaware of any injuries resulting from this defect.

### Pain Patches Still the Standard

Treating chronic pain with drugs in transdermal patches offers extended relief, so several companies are addressing known risks by using new patch technology to deliver drugs more safely.

The matrix patch design for Mylan's fentanyl patch, which the FDA approved in 2005, does not have the problem of leaks of medicine that caused recalls of other skin fentanyl patches. In Mylan's product, the drug fentanyl is in the adhesive instead of being enclosed in a pouch of liquid as found in reservoir patches.

Mylan is the only company that markets the matrix fentanyl patch in the U.S. and has not recalled it due to leakage because the matrix design cannot leak, company spokesman Michael Laffin said.

The company has about 56 percent of the fentanyl patch market, Chief Operating Officer Heather Bresch told *DGR*. "I see the patch market continuing to be a great market for us ... and I think the U.S. market will continue to grow," she said.

Steven Damon, Altea Therapeutics' vice president of business development, told *DGR* that his company is studying an approach using fentanyl citrate.

Altea's investigational product creates microscopic pores in the skin where fentanyl citrate enters the body. If someone else comes into contact with the patch, there is no risk of accidental drug exposure, Damon said. Altea's patch is much smaller than existing patches, potentially allowing the company to put larger doses in a single patch. — Elizabeth Jones, Elizabeth Collins

## Warning Letter, from Page 7

Sandoz did not complete investigations on time, as its standard operating procedure requires, for at least 15 products including hypertension drug lisinopril, painkiller fentanyl citrate lozenges and sedative-hypnotic drug alprazolam.

### Audit Trails

The company also was cited for not having a laboratory computer system that tracked the deletion of raw data or files.

According to the letter, the firm uses the Agilent Chemstation data acquisition system for the HP 8453 UV/Visible spectrophotometer, which is used for dissolution testing of finished product, stability samples and process- and method-validation studies.

The system allows Sandoz analysts to modify, overwrite and delete original data files without leaving an audit trail, the letter says.

“Your laboratory computer system lacks necessary controls to ensure that data is protected from tampering, and it also lacks audit trail capabilities to detect data that could be potentially compromised,” the FDA says.

The FDA was critical of Sandoz’s quality control unit in the letter, citing it for failing to ensure that manufacturing investigations were initiated and completed. The unit also was cited for failing to ensure that the manufacturing process for generic Toprol XL was adequately validated.

In addition, the quality control unit failed to review all data and results of in-process tests and did not incorporate manufacturing changes into the master batch record, the letter says.

The company would not say whether it plans to recall any products made at its Wilson facility and would not confirm whether it has any pending ANDAs referencing the site.

The warning letter can be accessed at [www.fda.gov/foi/warning\\_letters/s6891c.pdf](http://www.fda.gov/foi/warning_letters/s6891c.pdf).

— Christopher Hollis

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## Cracked Vials Cause Procrit Recall

Johnson & Johnson (J&J) subsidiary Ortho Biotech is recalling more than 44,000 vials of the erythropoiesis-stimulating agent Procrit because its post-manufacturing inspection found cracks in a small number of vials.

Only one lot is being recalled. It was distributed by J&J’s JOM Pharmaceutical Services warehouse between April 15 and July 17, the company says in a statement.

Other Procrit (epoetin alfa) lots distributed by JOM are not affected by the recall, which is being conducted in cooperation with the FDA, the company says. The amount being recalled is a small portion of the Procrit in distribution, and no supply disruptions are anticipated.

“Vials exhibiting even slight cracks may not maintain their sterile condition and should not be used for subcutaneous or [IV] injection,” Ortho Biotech says. — Christopher Hollis

**FDANEWS**
**Customer Service**

 (888) 838-5578 • +1 (703) 538-7600  
[customerservice@fdanews.com](mailto:customerservice@fdanews.com)
**Editor:** Christopher Hollis

 (703) 538-7650  
[chollis@fdanews.com](mailto:chollis@fdanews.com)
**Ad Sales:** Andrew McSherry

 (703) 538-7643  
[amcsherry@fdanews.com](mailto:amcsherry@fdanews.com)
**Content Sales:** Alka Desai

 (703) 538-7669  
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300 N. Washington St., Suite 200 • Falls Church, VA 22046-3431 • Phone: (888) 838-5578 • +1 (703) 538-7600 • Fax: +1 (703) 538-7676

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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,

*(See Data Pilot, Page 4)*

## 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](http://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](http://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

(See **EDC**, Page 4)

**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/Drug\\_Industry\\_Daily/SafeguardingAmericasPharmaceuticalsAct.pdf](http://www.fdanews.com/ext/files/Drug_Industry_Daily/SafeguardingAmericasPharmaceuticalsAct.pdf).

— Christopher Hollis, Mari Serebrov

## Data Pilot, from Page 1

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](http://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](http://www.fda.gov/oc/datacouncil/janus_operational_pilot.html). — Martin Gidron

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## EDC, from Page 2

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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**Customer Service**

 (888) 838-5578 • +1 (703) 538-7600  
[customerservice@fdanews.com](mailto:customerservice@fdanews.com)
**Editorial**

 (703) 538-7631  
[mserebrov@fdanews.com](mailto:mserebrov@fdanews.com)
**Ad Sales:** Andrew McSherry

 (703) 538-7643  
[amcsherry@fdanews.com](mailto:amcsherry@fdanews.com)
**Content Sales:** Alka Desai

 (703) 538-7669  
[adesai@fdanews.com](mailto:adesai@fdanews.com)

 300 N. Washington St., Suite 200 • Falls Church, VA 22046-3431 • Phone: (888) 838-5578 • +1 (703) 538-7600 • Fax: +1 (703) 538-7676  
[www.fdanews.com](http://www.fdanews.com)

**Reporters:** Martin Gidron, Christopher Hollis

**President:** Cynthia Carter; **Publisher:** Matt Salt; **Editorial Director:** David Grant; **Executive Editor:** Mari Serebrov

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