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**CMC**

**Post-approval changes often unnecessary, continuous improvement could avoid them; guidance in offing**

**By Joseph Pickett  
Managing Editor**

PHILADELPHIA — Many product changes made in the post-approval world are reactive in nature, usually due to FDA observations or product failure. These changes can be avoided through continuous improvement, such as, analysis of a database of manufacturing experiences, product process deviations and retrospective analysis to establish a design space, according to a senior CDER official.

Eric Duffy, Ph.D., director of

the Division of Postmarketing Evaluation, told the **Drug Information Assn. (DIA)** annual meeting that he is seeing a variety of regulatory approaches where firms are taking the lead to change and support change in terms of data and regulatory strategies.

"I think this global picture permits us to move forward to design a quality-assessment system. Good focus on post approval issues is a more effective way to move forward," he said.

[see Duffy, page 5]

**Compliance/enforcement**

**Patient harm not key in prosecutions, U.S. attorney says**

**By Jeannette Cezanne  
New England Correspondent**

CAMBRIDGE, MA — In the prosecution of violations of FDA regulations, harm to patients may be excluded from the judiciary process.

Those are startling words on the surface, but as James Sheehan, associate attorney in the U.S. Attorney's office in Philadelphia explained at an Aug. 22-24 FDA Regulatory and Compliance Symposium at **Harvard University**, it is one of the odd ways that the law works.

"The tools used to prosecute health-fraud cases are very different

from the tools on the regulatory side," Sheehan said. "The issues go to the integrity of the process." The successful prosecution of these cases rests on the ability to prove that the drug or medical device company's conduct was both illegal and intentional.

These issues carry certain ramifications that explain why harm to patients, seemingly at the core of medical-fraud prosecutions, is in a sense irrelevant.

The Department of Justice, via [see Sheehan, page 5]

**Electronic records****Part 11 risk assessment ‘not an alternative’ to compliance with predicate rules****By Joseph Pickett  
Managing Editor**

PHILADELPHIA — When conducting a risk assessment of computer systems for compliance with 21 CFR Part 11 pertaining to electronic records, it is important to think of risk in how it applies to your patient, product or safety. What you should not do is gauge risk based upon whether FDA has issued 483s in certain areas, because at that point you are conducting risk assessment on getting caught, said Harry Huss, director of compliance policy and program support services, **Charles River Labs**.

He added at the June DIA meeting here that despite FDA’s talk of Part 11 enforcement discretion and narrow interpretation, “FDA is making it clear they intend to enforce predicate rules,” he noted. “The agency feels they have all the ammunition they need to enforce virtually every aspect of Part 11, except for electronic signatures.”

FDAers he has spoken with, including Charles Snipes, Ph.D, director of CDER’s Division of Scientific Investigations, and Linda Tollefson, director of the Surveillance and Compliance at the Center for Veterinary Medicine, stated that they do not “feel hamstrung that Part 11 has been withdrawn.” They added that the current Good Laboratory Practice (GLP) guidelines “are really a template for Part 11 requirements.”

In a recent meeting with the aforementioned FDAers, he noted they pointed out to him: “If your risk assessment says you don’t need to validate something in the medical device area, you are in error.” He noted that FDA seems particularly

comfortable to give warning letters on Part 11 in medical devices.

“I often see us use the concept of risk assessment to mean that we need to do less validation, and often it means we need to do more,” he noted. Further, Huss stressed that firms must not base their risk assessment on the type of system. “I have been in companies where they said that they don’t validate spreadsheets. That’s dumb as hell. It’s how you use the system that is important, not the type of system.

***“I have been in companies where they said that they don’t validate spreadsheets. That’s dumb as hell. It’s how you use the system that is important, not the type of system.”***

“If you use an Excel spreadsheet to document how you dose neonates with a potentially toxic drug, yeah, validate the hell out of that one.”

Huss noted that a chief pathologist at a company he visited spent several minutes explaining how there was no need to validate a spreadsheet. “It’s just a spreadsheet, you plug in numbers and it tells you what the dose is,” the pathologist explained.

But then he noticed that one of the dosage algorithms was wrong because another pathologist had not changed the workbook title or the algorithm. “So for four studies, the patients got 10 times the dose they should have.” That is why you validate based upon use of the system, not type of system, he emphasized. Also, be sure to understand the type of record you are using, the executive said. “The fact that you can print out the document doesn’t mean you don’t have an electronic record.” For example, if you are doing body weights for 300 animals for 760 days,

you may be able to print out the results. But if the data was crunched by that system, it is an electronic record and Part 11 applies.

He added that while there is great anticipation for the Part 11 rewrite, he is not optimistic it will come out by the end of the summer, as promised by FDA most recently. “Some people on the Part 11 committee have told me, ‘when it’s published you’ll be as surprised as I am,’” he said.

Huss noted with interest that a Part 11 meeting that was scheduled for June 2004 was canceled due to the death of President Reagan, and was never re-scheduled. “I’ve never seen a meeting canceled so fast and not re-scheduled,” he quipped. He noted that the delay stems from the fact that FDA is trying not to offend anyone with the re-write. Also to blame are power struggles going on within the agency regarding the regulation of Part 11.

Regarding a petition sent to FDA last year by industry to withdraw Part 11, he noted, “it was terribly flawed and poorly thought through. Even the people most opposed to Part 11 at the agency couldn’t swallow it.” Predicate rules were left hanging out there, so the petition just fizzled out.

**Electronic records****Big pharma to begin rollout of SAFE electronic sig system in 2007****By Joseph Pickett  
Managing Editor**

PHILADELPHIA — The Secure Access For Everyone (SAFE) initiative — an industry effort to create a trusted, secure and legally enforceable electronic signature application for business and clinical transactions — will be rolled out more aggressively in the next two years as big pharma firms, such as, **Pfizer** and **GlaxoSmithKline** begin

implementation, a **Nextar Therapeutics** senior executive stated here June 20.

Tam Woodrum, senior director of IT quality and competence, told the DIA annual meeting that SAFE has met with some resistance because implementation has been slower than expected. "There are many laws between other states and countries governing the use of electronic signatures," he said. "Regulators want to make sure that the result is a legally enforceable signature."

**"There are many laws between other states and countries governing the use of electronic signatures," he said. "Regulators want to make sure that the result is a legally enforceable signature."**

However, the system is superior to a firm having its employees' signatures and initials registered with FDA. "SAFE is not just business-to-regulator, but also business-to-business, it is a central repository," he said. "The types of standards you have with SAFE is (sic) broader than with just business-to-regulator."

Woodrum noted that SAFE is essential because research shows that 40% of R&D costs involve handling paper. "There are a lot of possibilities to cut costs if we handle information electronically."

Also, there is a working group within industry that is working with FDA on SAFE. "One program is an auditor-familiarization program that is putting together a manual to walk auditor[s] through how SAFE works," he said. The next piece is how to move from this manual to an in-person training program. The manual is complete, and the first

meeting on the training materials was in May, with a second round of review occurring now. The goal, Woodrum noted, is to get the training program under six hours.

The working group also is compiling a compliance matrix that includes a series of scenarios and checklists that can be used on the validation side. It also includes an internal SOP matrix for the procedural controls, which she stressed "are not out-of-the-box compliant. You must have appropriate internal processes in place."

Also in the works is a European Agency for the Evaluation of Medicinal Products (EMA) pilot, the goal of which is to ensure the electronic signatures will be valid in Europe. EMA recently stated that the SAFE initiative "can be implemented in a way that is compatible with the European Union's digital signature directives," she said.

**"One program is an auditor-familiarization program that is putting together a manual to walk auditor[s] through how SAFE works," he said.**

Another pilot is being conducted with the National Cancer Institute (NCI), where form 1572 was worked through using 50 clinical investigators at eight clinical sites. The pilot now will be conducted on studies involving more than 13,000 patients.

Woodrum noted that there are "many partnerships underway" with other vendors to ensure that off-the-shelf systems work with SAFE.

Further, **Johnson&Johnson** is working with SAFE in ways other than electronic signatures — it is having its 78,000 employees use the system for authentication purposes.

## **Master planning Validation plan should include risk prioritization of all company systems, says Acambis quality exec**

**By Joseph Pickett  
Managing Editor**

ARLINGTON, VA — It is vital that a system-validation, master plan include a validation program for every computer system in a company, each of which should be prioritized according to risk, with a complete justification of that ranking, the quality director for **Acambis** stated here Aug. 18.

Felicia Ford-Rice, speaking at an **Institute of Validation Technology** conference, cautioned that it is important to conduct all validation programs listed in the master plan. "You can have a great plan on paper, but if you don't actually carry out the plan, FDA will not like it," she said. If yours is a new company, Ford-Rice added, it is okay if systems are not fully validated. "Just provide a schedule to the agency detailing how you are going to complete the validation of your systems. But you can't just write a plan and not do anything with it for years."

She advised that when providing FDA with a description of your firm's systems, you should put them into an attachment. "If you put this into the body of the document, it is very verbose."

According to the **Acambis** executive, a validation master plan organizes requirements according to human and technical resources, documentation and testing / implementation/maintenance. "The master plan lists and defines the systems and equipment requiring

validation, parameters to be validated and the regulatory risk,” she noted.

The master plan should provide an introduction, purpose and scope (including assumptions, inclusions, exclusions and limitations), a systems description, functional department tasks and responsibilities, acceptance criteria, and deviation policy and definitions.

Also, the validation master plan should feature the product life cycle, standards and regulatory requirements, timelines, risk assessment, required documentation, review and approval responsibilities, revalidation and references.

Ford-Rice also described the importance of a user requirement specification (URS), which describes how the computerized system is to perform. “The URS defines the required functions to be performed by the system, external interfaces, operating environment, time and cost constraints, performance with respect to speed, availability and response time, and physical security.

**“You would say it needs to be able to interact with system X,” Ford-Rice said.**

“The URS generally is the most problematic document because it involves the end user,” she said. While some in the industry describe the document as “blue sky,” “you don’t want to include requirements that cannot be met.”

One audience member asked that in a user requirement, if you have a computer system that has a lot of sensors that are related and are capturing data, do you put the sensors in the document?

“You would say it needs to be able to interact with system X. That system probably has its own requirements. You say that it needs to interact with that system to get the data you want.”

She also reminded participants that when you buy a computerized system, “you are buying a system, not a validated program.

You have to have that system in your environment using your data, and then validate it.”

## **RFID** **Technology seen as ‘holy grail’ in tracking products, improving product validation**

**By Jeannette Cezanne**  
**New England Correspondent**

CAMBRIDGE, MA — Radio-frequency identification (RFID), which FDA and industry have pushed as a means of thwarting counterfeiting of prescription and OTC drugs, was hailed at a conference here Aug. 24 as a means of also improving pharmaceutical manufacturing.

John McGrory, CEO of **Edge Dynamics**, Redwood City, CA, told the second annual FDA Regulatory and Compliance Symposium at Harvard that technology is a tremendous asset in managing complex pharmacology, distribution flows of product, money and information.

But mistakes can occur at any point along the flow from manufacturer to wholesaler to pharmacy to patient, including primary and secondary distribution and brokerage shipments.

“Robust channel commerce requires transparency, accountability and control,” McGrory said. “It can enable improvements in financial performance, regulatory compliance, market integrity and patient safety.”

Given that there are a number of compliance issues making it mandatory to follow certain procedures (whether because of the Sarbanes-Oxley Act, SEC reporting, government pricing, etc.), and that in commercial operations compliance comes into play in a number of areas, it becomes extremely expensive to *not* comply with regulations. Moreover, if there is poor data collection and

analysis, it moves regulators to wonder what else might be wrong in the company.

There’s no question that non-compliance can be expensive. McGrory cited the \$839 million in restitution levied on **Bristol-Myers Squibb** to defer prosecution on a charge of conspiring to commit securities fraud for the company’s failure to disclose its “channel-stuffing” activities in 2000 and 2001. Policy controls, including regulatory constraints, corporate objectives, trade agreements and market dynamics, ensure that companies found to be in violation will be prosecuted.

Any technology solution for pharmaceutical manufacturers needs to address all of these challenges. By capturing and validating all channel data, including orders in real-time, technology can build a complete and comprehensive system of record of the manufacturer’s distribution channel. This solution then analyzes the record to evaluate orders, balance inventory levels in the channel, manage service fill rates, limit unauthorized distribution and compensate wholesalers for the reporting services that they provide.

Each order processed must be documented for regulatory and auditing purposes and, to enhance patient safety, there has to be deep analysis of channel documents to detect unusual activities further downstream. Poor channel control can result in a number of byproducts, among them counterfeit drugs.

Enterprise technology needs to rise to the challenges of regulation and compliance, he said. Legacy technology provides very limited analytics; current-generation systems provide some analytics, but it’s the next-generation systems, thanks in part to extensive RFID use, which will provide deep real-time analytics.

An enterprise-class solution includes reliability, scalability, transactionability, auditability and compliance. All of these areas can be provided by the technology partner either as on-premise or as hosted

solutions, and all of them will ensure better accountability and responsibility for the industry.

Given all of this, “RFID is the holy grail,” said McGrory. The capability to identify and track products gives in turn the ability to accumulate and validate accurate data.

The visibility provided by this technology allows an accurate knowledge of the inventory level by eliminating the discrepancy between inventory record and physical inventory. RFID technology can prevent or reduce the sources of errors.

The important “pedigree” — the chain of custody document — now difficult to track, will be simplified and mechanized once RFID is used throughout the industry. Other benefits will include the reduction of labor costs, a simplification of business processes and a reduction in inventory inaccuracies.

## Duffy

### Continued from page 1

He noted that risk-based evaluation allows better use of resources, which is what FDA does when it receives submissions. “Submissions are triaged upon arrival and a risk assessment is made. We review the assignment based upon that assessment.” Duffy said that a primary issue at FDA is to facilitate implementation of newer technologies, which leads to the development of a knowledge framework.

He said that he does not see as much of that “good, solid development” through the NDA process. “This is reflected,” he noted, “by the fact that there are so many supplements that need to be implemented soon after approval.”

The agency has seen an increase in the number of supplements submitted within two years of approval. “Firms may not have been really equipped to move in the manufacturing setting,” he said.

Some of the more common deficiencies he has seen in supplements are:

- Revised or changed manufacturing process was inadequately described;
- Inadequate rationale for a change;
- Inadequate documentation on whether or not a control change is needed;
- Insufficient controls for incoming materials. “Several citations have been made on materials control,” he said;
- Justification for a specification not adequate; and,
- Stability of data analysis.

For drug products, Duffy continued, many of the same issues remain. Some of these are inadequate description of process, control of materials and labeling deficiencies. Submissions for cleaning validation also are not needed.

He added that many post-approval changes may not even be necessary to submit. “Some of the ones we see that are not needed include analytical site changes; stability-testing, site changes; and packaging site changes.”

Finally, Duffy stated: “Our analysis of post-approval submissions will result in a guidance to permit everyone to have a common understanding of new approaches.” He did not mention when this guidance would be published.

## Sheehan

### Continued from page 1

the U.S. Attorney’s office, looks at fraud specifically as it relates both to FDA and to payer programs. Investigating FDA fraud involves answering several questions, according to Sheehan.

How did the product (medicine or medical device) *get* approved? This question usually involves false statements about clinical trials. They can include questions about the product’s reported results (product efficacy, number of adverse events (AEs) associated with trials), the company’s compliance with

protocol (including patient selection and endpoints), and participant protections.

The second question is: how did the product obtain approval? Two thousand AEs go unreported every year, and here, noted Sheehan, case law is significantly helpful: in *U.S. v. Caputo*, the “defendant intentionally avoided information about potential safety hazards,” while in a 2004 Massachusetts case, a product was said to be misbranded “if,” said Sheehan, “you knew the product was likely to fail more frequently than disclosed in your labeling and you do not disclose (that) to FDA.”

Fraud on payer programs is, Sheehan noted, a “growing area of liability.” Payers rely on the labeling and on FDA approval as the basis for making payments. The development of relationships between salespeople and decision-makers, while nothing new, is being better scrutinized, especially when occurring on a larger scale than in the past. Kickbacks are not uncommon, and nor are “payments to physicians, health plans, advisory panels, PBMs [pharmacy benefit managers] and pharmacy directors to advocate for, promote or write for a given product.” In 2005, for example, the chief pharmacist of the Pennsylvania Department of Welfare was fined \$27,000 for accepting money from **Pfizer** while serving on a state committee selecting drugs.

The **Schering-Plough** GMP consent decree in 2002 set case law for fraud on payers in the situation where the product or the quality of the product are not as advertised. “The disclosure/false claims can be for the same product,” noted Sheehan; the two prosecutions do not need to be separate. On the other hand, “the fraud statutes on false claims is (sic) the oldest and most extensive case law, so it is used more.”

And, he said, this is where the issue of human harm comes into the equation. Sheehan said prosecutors look first at where the most successfully prosecuted cases were — what he

called “looking in the rearview mirror to know where to go next.”

By and large, these successes have been in the false claims arena, Sheehan added. In focusing on intent, the Department of Justice is focusing on false and/or misleading information, and intent is far easier to

prove in those cases than it is in human-harm ones. Whistleblowers who come to the U.S. Attorney are told immediately that their first step must be the company’s compliance division, because once compliance has been informed of the wrongdoing, the company can no longer assert that it didn’t know about it, and intent can

be established.

These are the cases that are most successful. They are “less complex and easier to put together,” said Sheehan, thus making it possible that harm to patients — the logical focus of the prosecutions — might be excluded from the judicial process altogether.

**Analysis of 483s/EIRs for GMP validation issues**  
**By Joseph Pickett, Managing Editor**

**Human drugs**

**23-item 483 for Allergy Labs citing aseptic processing, sanitation procedures, equipment cleaning**

**Allergy Laboratories**, Oklahoma City, received a 23-item 483 for its sterile drug manufacturing facilities because its aseptic processing areas were deficient regarding the system for monitoring environmental conditions. Further, its written procedures for sanitation were not followed, according to FDA records. The report also documented numerous failures in the cleaning and maintenance of equipment.

The firm further received a 20-item 483 following an inspection of its allergenic extract manufacturing facilities (see below). Only the 483s were available as this publication went to press.

The sterile drugs audit, prepared by FDA investigators Margaret Annes and Lloyd Payne from the Dallas District Office, revealed that Allergy’s environmental sampling of non-viable and viable particulates in two undisclosed production areas were not adequate to determine the air and surface qualities. Also, “environmental surface monitoring of viable particulates in the [undisclosed] Vial Wash Room and Sterile Gowning Room is performed [at incorrect intervals].”

The FDAers also found the firm to be deficient in its written procedures for cleaning and maintenance. For example, “the firm has not validated the procedures used to clean and sanitize the processing equipment and production areas,” according to the 483. Also, a finalized validation report for the ephedrine sulfate injection USP drug product was not developed.

In addition, “written procedures for cleaning and maintenance failed to include parameters relevant to the operation.”

Further, the report documented that the cleaning and sanitizing validation report for the phenylephrine hydrochloride injection USP and L-cysteine hydrochloride injection USP did not include suitability studies for the use of an undisclosed method for detecting phenylephrine hydrochloride and L-cysteine hydrochloride following the cleaning process to ensure that no drug residues were present.

Also, procedures for the cleaning and maintenance of equipment were deficient regarding maintenance and cleaning schedules, including sanitizing schedules. For example, “the firm has not established a written procedure to prevent drug product contamination,” the 483 stated.

Further, the bulk drug solution mixing tanks were not cleaned and sanitized prior to being placed into the Vial Wash Room from a non-classified storage area. Next, “procedures for the cleaning and maintenance of equipment are deficient regarding the protection of clean equipment from contamination prior to use.” For example, the bulk drug solution mixing tanks were not covered or held in a manner that would prevent environmental contamination while being stored in a non-classified storage following cleaning.

The company also was cited because “equipment used in the manufacture, processing, packing or holding of drug products is not of appropriate design to facilitate operations for its intended use and cleaning and maintenance.” Specifically, the water for injection system was designed or constructed of a material that could promote microbial contamination of the finished product. Further, there was clear, flexible plastic tubing used to connect an undisclosed part to the water for injection storage tank at one sample port. This resulted in a biofilm on the interior surface of the tubing.

In addition, sampling and testing plans for drug products were not described in written procedures, which included the method of sampling and number of units per batch to be tested. “Specifically, the firm does not have an SOP that addresses out-of-specification (OOS) investigations conducted by contract labs. There is no SOP that allow[s] the firm to re-test or re-sample a drug component if the initial tests from the contract lab indicate the product does not conform to specifications.”

The next violation in the 483 noted that actual yield and percentages of theoretical yield were not determined at the conclusion of each appropriate phase of manufacturing the drug product. For example, the 483 stated, “the firm is not reconciling the use of the bulk solution during filling operations. The firm does not document the amount of bulk solution left in the carboy after filling operations have been completed.”

Also, the company did not determine the theoretical amount of vials that were to be filled from the bulk solution that was manufactured, and it did not compare the theoretical vs. actual yields of filled vials to determine if an investigation was required.

- ✓ **The Checklist — Allergy Laboratories**
- ✓ **Aseptic processing flaws**
- ✓ **Written sanitation procedures not followed**

Further, Allergy’s written records of major equipment cleaning and use were not included in individual equipment logs. For example, “The firm does not document the use and cleaning of their mixing tanks in individual equipment logs. The firm does not have dedicated mixing tanks for the Ephedrine Sulfate Injection USP...”

In the second inspection, investigators Julie Bringger and Jennifer Bridgewater from Center for Drugs also found that the firm lacked validation studies to support the current packaging and shipping practices. “Packaging and shipping conditions consist of placing the extracts in uninsulated cardboard boxes wrapped with a thin plastic strip, placing Styrofoam chips throughout the box and shipping the final container un-refrigerated to the customer,” the report noted. There was no assurance by Allergy Labs that this shipping procedure maintained final product at the labeled temperature.

Further, the report noted the following violations relating to cleanroom practices and conditions:

- Personnel performing sterility testing were observed with exposed skin;
- A technician was seen sanitizing hands immediately before touching finger touch plates used for personnel monitoring;
- A technician was observed adjusting cleanroom clothing;
- There was no assurance that the results obtained from the surface monitoring of the laminar air-flow (LAF) hoods were valid;
- The base of the viable air-monitoring devices utilized in the sterile filling area were rusty and exhibited flaking paint;
- Personnel were observed wiping the surface of the LAF hood after filling final product and prior to performing surface monitoring.

In the materials system, the audit noted: “There are no incoming checks or specifications for filters used in sterile filtration and tubing used in the manufacturing of allergenic extracts.”

Also, there were no incoming checks for petri dishes utilized in preparation of environmental-monitoring plates. The firm could not be reached for comment. **Allergy Laboratories, Oklahoma City, 8/9-29/05, 10/3-7, 25/05, Doc. 109855M, \$6 plus retrieval.**

## Lack of acceptance criteria and validation flaws nets 6-item 483 for American I.V.

**American I.V. Products** (AIV), Hanover, MD, was hit with a six-item 483 because it failed to establish acceptance criteria prior to the performance of validation activities, and also prior to the performance of verification activities.

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Conducting the inspection was investigator Lori Lawless from the Baltimore District Office. The EIR was not available as this publication went to press. The report stated that American I.V. could not provide a protocol or previously established acceptance criteria for the performance of validation tests used to determine if the design inputs met user needs.

Next, the firm “could not provide a protocol or previously established acceptance criteria for the testing of the ultrasound transducers...this testing was designated as design verification used to determine if the design inputs met design inputs,” according to the EIR.

The company’s written response stated: “The protocol for validating the device design for AIV FMTs has been written and approved. The provided protocol will be the template for future design validation protocols.” Also, American I.V. noted that for future device developments, “there is a requirement to develop documented validation protocols for testing production units under actual or simulated use conditions. The protocol will ensure that the devices conform to defined user needs and intended users.”

Also, a process whose results could not be fully verified by subsequent inspection and test was not validated and approved according to established procedures. “Specifically, the firm does not have a protocol for, nor has performed, the process validation for their manufacturing process used to manufacture the FMT 10834 ultrasound fetal monitor transducers,” the report stated.

Next, the firm responded that formal specifications for the fetal monitoring devices, including acceptance criteria, were written and approved in April 2005. “We feel that to go back and create written protocols for the previous [undisclosed] testing does not add any value to the program at this time.”

- ✓ **The Checklist — American I.V.**
- ✓ **Acceptance criteria not established**
- ✓ **OOS procedures not followed**

Next, procedures were not followed for the control of products that did not conform to specifications. For example, one of the firm’s work instructions lacked documentation that undisclosed non-conformities were identified or investigated. In another work instruction, “there is no documentation that the non-conformity [pertaining to PCB boards] was identified or investigated. The PCB boards are used to manufacture fetal monitor transducers.”

American I.V. stated in response that it had designed a protocol to validate the transducers in question. “For future medical devices,” the company noted, “protocols will be written and production/manufacturing process validated to that protocol. This process has been implemented by the company.”

Next, the device history record did not include the primary identification labels and labeling for each device. For example, “the device history records for kits...manufactured from March 10, 2005, through July 25, 2005, do not include

the labeling that is attached to the transducer. The records do not include the labeling that is applied to the final packaging.”

American I.V. noted in response: “The lack of device and packaging labels in the device history record was immediately addressed during the facility inspection. Copies of the labels...were placed in the device history record...and copies of labeling for kits manufactured after number [undisclosed] were made from units that were found in inventory.”

In response to the firm’s corrections, FDA wrote: “These documents appear to address the observations found in the 483...Corrective actions taken will be verified during your next inspection.”

**American I.V. Products, Hanover, MD, 7/29-8/17/05, Doc. 109857M, \$6.50 plus retrieval.**

## Andrx Pharma on receiving end of 9-item 483 for OOS, QC violations, control procedures

**Andrx Pharmaceuticals**, Ft. Lauderdale, FL, was slapped with a nine-item 483 in a March-April inspection because it did not perform investigations of OOS results. Also, the firm’s quality control unit was inadequate, and the firm had faulty control procedures, which did not validate the performance of manufacturing processes.

The audit was performed by investigators Ileana Barreto-Pettit, Jennifer Menendez, Rebeca Rodriguez and analyst Jennifer Hollstrom from FDA’s Maitland, FL, District Office. The EIR was not available at press time.

According to the report, Andrx failed “to thoroughly review any unexplained discrepancy and the failure of a batch or any of its components to meet any of its specifications whether or not the batch has been thoroughly distributed.”

Specifically, the firm did not perform adequate investigations with scientifically justifiable conclusions to incidents of OOS results or production deviations and/or failed to implement appropriate corrective actions for the root cause determination.

The report stated that the QC unit “failed to adequately review Ketoprofen Validation Protocol and Report No. 002PV005 and, as a result, it released and distributed between March and July 2005 six batches of Ketoprofen ER capsules (lot #'s: 520E017, 520F0368, 520E018, F520F0840, F520F1030, and F520F1031) that were manufactured with a process that showed significant variability and was not adequately validated.”

Next, the QC unit did not ensure that Phase I Laboratory Investigations were adequately investigated, documented and trended after they were removed from an undisclosed system in September 2005 and transferred to a manual logbook.

Regarding control procedures, FDA documents noted that the QC unit approved Doc. No. 0002PV05 titled

“Process Validation Protocol — Manufacture of Ketoprofen” to evaluate the accuracy of scale reading versus an undisclosed type of reading for the sustained-release coating process as the difference in dissolution performance at the eighth hour.

FDA added: “Five commercial batches of [an undisclosed product] were manufactured under this validation protocol, which resulted in three batches (52050, 55797 & 520E018, subplot#4) that failed dissolution specifications at the eighth hour, and a batch (57043) that deviated from the target capsule fill weight specified in the manufacturing batch record in order to meet dissolution specification at the eighth hour.”

Next, FDA cited the use of instruments and apparatus not meeting established specifications. “Specifically, in December 2005,” the report stated, “the QC unit determined the need to replace the flow rate valves of all [undisclosed] apparatuses as a result of frequent clogging, flow rate problems and increased bubble formation that randomly caused ‘erratic’ dissolution results.”

- ✓ **The Checklist — Andrx Pharmaceuticals**
- ✓ **Quality audits inadequate**
- ✓ **No corrective actions for OOS results**

However, the quality unit failed to adequately monitor the implementation of its corrective action and, as a result, the valves were not installed and the use of these dissolution baths with potentially malfunctioning valves continued for dissolution testing of all cartia, diltia, taztia, metformin, naproxen sodium, and ketoprofen drug products.”

Further, written records of investigations into unexplained discrepancies did not include the conclusions and follow-up. For example, the 483 stated, “the cleaning swab failure investigations reported under TWRs 1545, 1555, 2194, 2259 disclosed that the root cause was the failure to thoroughly rinse or clean equipment or that the cleaning procedures were not specific enough.”

The agency added that the QC unit also failed to follow up on these findings and none of the SOPs involved in these investigations had been revised to make the rinsing and/or cleaning instructions more specific.

Additionally, the FDAers wrote, “there is a failure to thoroughly review any unexplained discrepancy and the failure of a batch or any of its components to meet any of its specifications whether or not the batch has been thoroughly distributed.”

Specifically, the firm did not perform adequate investigations with scientifically justifiable conclusions to incidents of OOS results or production deviations and/or failed to implement appropriate corrective actions for the root-cause determination.

The deficiencies included the following: The investigation report TWR #1691 for finished product testing

of metformin HCl extended-release tablets, 500 mg lot no. F571F0692 was specifically for content uniformity testing. During analytical testing, one of the capsules failed to meet the Stage 1 established specification of an undisclosed ingredient label claim and another tablet was toward the low end of the specification range.

The root-cause analysis indicated analyst error and two additional capsules were extracted with the results replacing the original OOS capsules, the 483 stated. The investigation revealed that the analyst observed a gelatin like mass of material at the bottom of one of the flasks and a piece of undissolved gel at the bottom of the other flask after adding diluting solvent A.

As a result, these two flasks were stirred for an additional 60 minutes, which is longer than the procedure or the eight other flasks, according to FDA documents. The analyst who performed the QC method transfer stressed the importance of full tablet disintegration before adding diluting solvent A or the material will clump. “The firm concluded that based on the physical observation of the two stock solutions in question proper active extraction did not take place.”

Following the audit, Andrx said in a press release that it “provided FDA with a detailed response to the 483, which included a proposed corrective action plan. FDA has not commented on the company’s response or corrective action plan. Andrx is working to resolve the cGMP issues at its facility as quickly as possible. The timing of that resolution is uncertain, and is not solely in our control.”

**Andrx Pharmaceuticals, Ft. Lauderdale, FL,  
3/16-4/18/06, Doc. 109849M, \$5.50 plus retrieval.**

- ✓ **Warning Letter Analysis —  
Details of key FDA warning letters  
released in July 2006 that contain  
citations for validation issues. Each letter  
is \$7 plus retrieval.  
By Michele Duarte and Joseph Pickett**

### Human drugs

## **Several firms receive warning letters for questionable erectile dysfunction drug claims, including sildenafil**

FDA in July dispatched several warning letters to firms that, according to the agency, have been making false claims about erectile dysfunction drugs. The following firms were cited:

### Access Financial, Bloomington, MN

FDA objected to the firm's marketing of the product Libidus on its website. According to the warning letter, a laboratory analysis conducted by FDA concluded that Libidus contains acetildenafil, an analogue of sildenafil. Sildenafil is the active pharmaceutical ingredient (API) in **Pfizer's** Viagra, an FDA-approved drug that is used to treat erectile dysfunction. Thus, the product is a drug for which Access Financial had not filed an NDA.

Additionally, the agency stated in the July 11 letter that it objected to various statements made on Access Financial's website describing Libidus, including, but not limited to: "So while erectile dysfunction (ED) drugs like Viagra, Cialis (sic) and Levitra treat impotency by redirecting blood flow, Libidus goes one step further by also fixing the problem at the libido level"; "Your penis will become engorged to give better pleasure to your lover"; "Your erection will be firm, and your penis will be rock hard...for as long as you desire." No comment was forthcoming from the firm before deadline. **Doc. 13906W**

### ATCSF, San Francisco

FDA objected in the July 11 warning letter to the company's marketing of the product Neophase on its website. According to the warning letter, a laboratory analysis conducted by FDA concluded that Neophase contains homosildenafil, an analogue of sildenafil. Sildenafil is the API in **Pfizer's** Viagra, an FDA-approved drug that is used to treat erectile dysfunction. Thus, the product is a drug for which ATCSF has not filed an NDA.

Additionally, FDA noted that the product labeling for Neophase does not declare that it contains homosildenafil. And, neither the product labeling nor the website list any negative side effects, such as, the fact that patients who take nitrates and consume Neophase are at risk of life-threatening hypotension, as well as other side effects associated with ED drugs.

The firm could not be contacted for comment.

**Doc. 13907W**

### Herbal Remedies, Casper, WY

FDA objected to the firm's marketing of the product Zimaxx on its website. According to the warning letter, a laboratory analysis conducted by FDA concluded that Zimaxx contains sildenafil, the API in **Pfizer's** Viagra, an FDA-approved drug that is used to treat erectile dysfunction. Thus, the product is a drug for which Herbal Remedies had not filed an NDA.

Additionally, the agency objected in the July 12 warning letter to various statements made on Herbal Remedies' website describing Zimaxx, including: "[Zimaxx] may help to achieve maximum results from lack of sexual desire dysfunction performance stamina and vitality"; "Zimaxx Viga' helps increase blood flow to the lower extremities and therefore help sexually dysfunctional men

perform normally"; and, "Zimaxx Viga' produces firmer and longer lasting erections."

"These statements suggest that your product does not contain sildenafil," FDA stressed. "They also falsely suggest that the product does not have the potential to cause side effects." The company could not be reached for comment. **Doc. 13916W**

### Herbin Tonics, LLC, Beverly Hills, CA

FDA objected to the company's marketing of the product Nasutra on its website. According to the warning letter, a laboratory analysis conducted by FDA concluded that Nasutra contains acetildenafil, an analogue of sildenafil. Sildenafil is the API in **Pfizer's** Viagra, an FDA-approved drug that is used to treat erectile dysfunction. Thus, the product is a drug for which Herbin Tonics had not filed an NDA.

And, the July 11 letter noted, neither the product labeling nor the website list any negative side effects, such as, the fact that patients who take nitrates and consume Nasutra are at risk of life-threatening hypotension, as well as other side effects associated with ED drugs. The firm was not available for comment. **Doc. 13917W**

### OSU Corp., Beverly Hills, CA

FDA objected to the company's marketing of the product Actra-Rx on its website. According to the warning letter, a laboratory analysis conducted by FDA concluded that Actra-Rx contains methisosildenafil, an analogue of sildenafil. Sildenafil is the API in **Pfizer's** Viagra, an FDA-approved drug that is used to treat erectile dysfunction. Thus, the product is a drug for which OSU had not filed an NDA.

Additionally, the agency objected in the July 11 letter to various statements made on OSU's website describing Actra-Rx, including, but not limited to: "Actra-Rx helps diabetics hypertension high blood pressure"; "Actra-Rx is the most effective and safest natural erection producing natural drug that promotes a completely safe and healthy, and all natural transformation"; "Rock hard erections guaranteed"; and "Experience the joy of longer and harder erections."

FDA also pointed out that the product labeling does not declare that Actra-Rx contains methisosildenafil. And, the website also states that Actra-Rx "has no side effects and is extremely effective for diabetics and very safe for persons suffering from hypertension," even though methisosildenafil likely exhibits similar pharmacological action to sildenafil. The company could not be reached for comment.

**Doc. 13918W**

### Robert Sargent, Batavia, NY

FDA objected to Sargent's marketing of the product Vigor-25 on his website. According to the warning letter, a laboratory analysis conducted by FDA concluded that Vigor-25 contains piperildenafil, an analogue of vardenafil. Vardenafil is the API in **GlaxoSmithKline's** Levitra, an FDA-approved drug that is used to treat erectile dysfunction. Thus, although Sargent markets Vigor-25 on his website as an

“herbal sex enhancement,” FDA pointed out that the product is a drug for which Sargent had not filed an NDA.

Similarly, the agency objected to various statements made on Sargent’s website describing Vigor-25, including, but not limited to: “Vigor-25 Male Potency is an herbal supplement developed to help boost your sexual pleasure and improve your sexual performance”; “Vigor-25 is a complete herbal supplement and works in as quickly as 25 minutes”; and, “Vigor25 gives you the stamina and energy you need when You need it.” The company was not available for comment. **Doc. 13919W**

## Concord Labs nets letter for faulty investigations

A Feb. 23 through March 22, FDA investigation of the **Concord Labs**, Fairfield, NJ, the maker of colchicine tablets, hyoscyamine sulfate tablets and nitroglycerin sublingual tablets, documented deviations from current GMP regulations.

Deviations noted in the July 11 letter included that written records were not always made of investigations into unexplained discrepancies, nor did investigations of unexplained discrepancies extend to other batches of the same drug product or other drug products that may have been associated with specific failures or discrepancies.

For example, product samples tested in conjunction with a complaint regarding loose caps on nitroglycerin tablets produced OOS results for assay and content uniformity.

And, the company did not perform further examination of product retains or a review of the batch record. Thus, the sample results were invalidated due to product damage from environmental exposure; but, FDA noted, there was no provision for this in the firm’s written procedures.

Concord also was hit with failure to maintain separate or defined areas or other such control systems necessary to prevent contamination and mix-ups in the course of manufacturing and processing operations; and failure to provide adequate measures to control air contamination and recirculation of dust from production areas where air was recirculated.

For example, no monitoring of the system was conducted to demonstrate that the volume of air supplied was sufficient to maintain appropriate air pressure differentials between manufacturing rooms, corridors and pharmacy rooms; and, no studies were conducted to assure that the system removed contaminants from the production area and that cross-contamination did not occur. Further, modifications made to the air-handling systems of production rooms, to add exhaust ventilation, were not validated to show their effectiveness at the time of installation.

Other violations included failure to establish master production and control records for each drug product, including statements of the maximum and minimum percentages of theoretical yields; use of deficient test devices for which apparatus did not meeting established

specifications; and, inadequate qualification studies for room temperature stability.

Finally, the company was cited for failure to maintain equipment at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality or purity of the drug products. **Doc. 13909W**

## Sheffield cited for OOS, QC flaws

An Oct. 17-19, 2005, inspection of **Sheffield Labs**, New London, CT, found significant deviations from FDA’s current GMP regulations for finished pharmaceuticals.

Significant deviations included failure of the QC unit to have adequate written procedures to ensure that product failures, failure investigation results, OOS results and stability failures were properly communicated to clients with whom the manufacturer contracted its products.

Sheffield also was cited in the July 24 warning letter for failure of its QC unit to be responsible for approving all procedures and specifications impacting on the identity, strength, quality and purity of drug products.

For example, FDA emphasized that Sheffield’s QC unit did not review or approve the analytical methods used to analyze the debriding ointment, cervical cream, lidocaine hydrochloride, hydrocortisone acetate and capsaicin products it contracted out, nor did its QC unit assure that these methods were properly validated.

Finally, the agency pointed out that Sheffield failed to establish the reliability of the suppliers’ test results through full testing; failed to evaluate the QS of each drug product to determine the need for changes in drug product specifications or manufacturing procedures; and failed to file NDAs for amino acid cervical cream and papain-urea-chlorophyllin ointment, which are considered new drugs. FDA noted as well that there were no adequate directions for the aforementioned products to ensure in the PIs that these products were safe for their intended uses.

The agency acknowledged written responses from Sheffield dated Nov. 2, 2005, and Jan. 6, 2006, but found them inadequate in that they did not provide timetables for all of the proposed CAPAs [corrective and preventive actions] in the letters. Sheffield also completely failed to address several of the investigational observations, FDA added. The firm was not available for comment.

**Doc. 13920W**

### Medical devices

## QS failures lead to warning letter for BioGenex

During an FDA investigation of **BioGenex Labs**, San Ramon, CA, conducted from Feb. 1 through March 9, the agency determined that the manufacturer of pathology

related stains, antibodies and in vitro diagnostic test kits was not in conformance with current GMP requirements of QS regulations for medical devices. Significant deviations included, but were not limited to the following.

BioGenex was cited in the July 27 warning letter for failure of management with executive responsibility to ensure that an adequate and effective QS had been fully implemented and maintained at all levels of the organization; failure to control products that did not conform to specifications; failure to establish procedures for the control of finished devices to ensure that only devices approved for release were distributed; and failure to establish procedures to control the design of the device to ensure that specified design requirements were met.

The agency acknowledged written response letters from BioGenex, dated March 30 and May 25, but concluded that the responses were inadequate because the specific documentation to demonstrate the implementation of CAPA had not been provided by the company. The firm could not be reached for comment.

**Doc. 13922W**

## Cardiac Science cited for failure to control non-conforming products

During an FDA investigation of **Cardiac Science's** Deerfield, WI-location, April 11— 26, FDA determined the manufacturer of automated external defibrillators was not in conformance with the current GMP requirements of the QS regulation for medical devices.

Violations included in the July 27 letter included failure to adequately maintain procedures to control products that did not conform to specified requirements and failure to adequately maintain procedures for rework to ensure that the products met current, approved specifications.

Cardiac Science was further audited for neglecting to adequately validate and approve according to established procedures processes that could not be fully verified by subsequent inspections and tests.

For example, Printed Circuit Board Assembly 120-2060-002 was not validated after changes were made and the Rev C board was released for production on April 23, 2004, FDA noted. The company was not available for comment.

**Doc. 13924W**

## Care Products slapped with letter for complaint procedures

Between June 12 and 16, FDA investigators determined that **Care Products**, McAllen TX, a manufacturer and distributor of shower gurneys/wheeled stretchers, shower chairs, manual mechanical walkers and

chairs, and low resident (safety) beds, was not in conformance with the current GMP requirements of the QS regulation for medical devices.

QS regulation violations noted during the inspection and in the July 10 warning letter included failure to establish adequate complaint-handling (C-H) procedures for receiving, reviewing, evaluating and documenting complaints by a formally designated unit.

Care Products was further cited for failure to analyze processes, work operations, concessions, quality audit reports, service records, returned products and other sources of quality data to identify existing and potential causes of nonconforming product or other quality problems; and, for failure to establish adequate procedures for the identification, documentation, validation or verification, review and approval of design changes before their implementation.

The agency pointed out that Care Products neglected to establish any written, C-H procedures; maintain records of complaints the firm received for the past eight years; maintain an electronic, complaint database; use a complaint form to document sources of information to report a femur fracture injury that occurred in a nursing home after a used firm's Model 740 shower gurney; or, document appropriate justification for not reporting the complaint of a femur fracture injury to FDA and not maintaining any complaints that represented an MDR [manufacturing device report]-reportable events in a separate file.

According to the warning letter, the firm also failed to maintain product procedures, including procedures for inspections, tests or verification activities for acceptance of incoming product; procedures to control product that did not conform to specified requirements; procedures to ensure that device history records for each batch, lot or unit were maintained to demonstrate that devices were manufactured in accordance with the device master record; or, procedures for quality audits.

In the warning letter, FDA emphasized that it "recognizes that your firm tried to obtain additional information regarding the use of your product and the circumstances of the patient fall through your distributor and your own insurance company." But, the agency added, "Your firm cannot delay reporting the medical AE to FDA. Regardless of whether the fall was due to a potential user error in letting the side rail down, a potential defective locking mechanism or a potential design weakness in the locking mechanism, your firm should have submitted an initial MDR injury report to FDA by June 2, 2006, within 30 days of first becoming aware of the medical AE."

FDA acknowledged the firm's response letters dated June 19 and June 29, but concluded that they were inadequate in that Care Products had not implemented a CAPA by which required, specific actions, with expected timeframes, would take place correct the deficiencies initially noted by the agency. The firm could not be contacted for comment before deadline. **Doc. 13925W**