REGULATORY

FDA Opens Door to RFID Packaging

The Food and Drug Administration announced in November an initiative that would implement radio frequency identification (RFID) technology to curb counterfeit-drug trafficking in the nation's pharmaceutical supply chain.

RFID relies on microchips embedded in labels and tags that can store a substantial amount of information and provide the ability to track and trace a package through a supply chain (depending on the type of RFID tag used). Although the technology has been used for years now in the retail supply chain and as a payment device in gas stations and tollbooths, RFID has not caught on as fast in the pharmaceutical industry.

According to Acting FDA Commissioner Lester M. Crawford, "In recent years, bogus medication has become a growing public health threat, because of the counterfeiters' ability to infiltrate our drug distribution system with worthless copies that look exactly like the authentic FDA-approved products."

Crawford explained in a media conference call that FDA officials have had a tough time identifying counterfeit products and tracing them back to the points of entry into the supply chain. "We are issuing a compliance policy guide that makes clear to industry that studies involving the use of RFID tags, chips, and antennas on drug containers can be conducted without special request for FDA authorization," Crawford said. "It will not result in an enforcement action on existing rules governing labeling, in so far as they are triggered by RFID technology."

This policy will remain in effect until 31 December 2007, allowing companies time to become familiar with the technology and run pilot programs incorporating RFID tags. FDA officials said that they expect drug manufacturers and distributors to use the technology's track-and-trace feature to establish an electronic pedigree "for products that are most likely to be counterfeited from the point of manufacturing to the point of dispensing," Crawford said. FDA made it clear that this initiative is not a mandate. Rather, the agency is relaxing its labeling rules, as they pertain to RFID, to allow companies to explore and pilot the technology

Companies such as Pfizer (New York, NY), Purdue Pharma (Stamford, CT), and GlaxoSmithKline (Philadelphia, PA) already have announced that they will ship some of their high-risk drugs with RFID tags. According to a press release issued by Pfizer, the company will add passive RFID tags to cases and retail packages of Viagra at an estimated initial cost of several million dollars. Pfizer doesn't expect to achieve any cost savings at this point.

"Drug counterfeiting is a serious problem, and RFID offers the potential to be an important anti-counterfeiting technology of the future," stated Tom Phillips, vice-president of the US Trade group for Pfizer. "It's certainly not the only solution. Changes to state regulations, more stringent licensing of pharmaceutical wholesalers, modifications of business practices, and increased enforcement also are very important. But RFID does offer a great promise as an effective tool in the battle against counterfeiting."

For Purdue Pharma, this pilot will not just be a "slap and ship" project, says Charles Nardi, executive director of corporate and supply chain systems. RFID technology will be fully integrated into the company's manufacturing cycle. The data on the RFID tags will include the item's global trade identification number, serial number, and business information such as individual production orders and sales orders. This creates a virtual license plate for the product, allowing the company to track a bevy of information about each shipment.

Purdue Pharma will ship 100-tablet bottles of OxyContin and Palladone with Class 0 (read only) RFID tags to two of its largest customers, Wal-Mart and H.D. Smith.

Wal-Mart is no stranger to RFID. The retail giant has mandated that its top 100 vendors switch from standard barcode labeling to RFID by early 2005. Although the Wal-Mart directive calls for pallet-level tagging, pharmaceutical companies hope to eventually tag individual items for increased security.

"What we will be seeing is RFID at a package level," says Dan Mullen, president of AIM Global (Warrendale, PA). "We are going to see tags on more finite, granular packaging. Where there is security or safety reasons, or where the value of the item is such that the need for the data justifies the cost of the tag, particularly in pharmaceuticals, electronics and higher-end apparel."

By placing track-and-trace RFID tags on individual items, the pharmaceutical industry will eventually be able to electronically track the pedigree of a drug from creation to purchase more easily than with the paperwork used today. "There is a statutory requirement (and in Florida a state requirement) for paper pedigree, which [may be] very expensive for the industry," says William Hubbard, FDA associate commissioner of policy and planning. "A technology like RFID could provide the kind of protection that paper pedigree would institute, but with much greater security." The high cost of RFID tags (20 to 50 cents as opposed to a 2-cent barcode), however, might prohibit companies from fully implementing e-pedigree program on a full-scale level at this time.

–George Koroneos

BIOTECH MANUFACTURING

Increasing Protein Production with Chloroplasts

Chlorogen, Inc. and Sigma-Aldrich Corporation, both based in St. Louis, Missouri, have entered into an agreement to produce proteins in the chloroplasts of tobacco plants. By using chloroplast transformation technology (CTT), the companies believe they will be able to produce transgenic proteins at significantly higher output rates and lower costs than can be achieved using current methods.

Current plant-based protein production involves introducing a new gene into the cell nucleus. In CTT, a new gene is inserted into approximately 100 chloroplasts within a plant cell, using standard biolistics technology. Because each chloroplast contains approximately 100 copies of its own genetic data, chloroplast transformation technology has the potential to produce as many as 10,000 copies of the introduced gene per plant cell. "We call this 'hyper expression,'" says David N. Duncan, PhD, president and CEO of Chlorogen.

Duncan explains that the choice of tobacco plants adds to the company's ability to produce large amounts of proteins quickly. "Next to sugar cane, tobacco produces more biomass per season on an acre of land than any other plant," he says. The large number of leaves and the extensive genetic copies available in the chloroplasts can help generate high levels of the expressed proteins. In addition, Duncan explains, tobacco is a prolific producer of seeds for the next year's crop. "We can go from a gene construct to a million seeds in just one year, which is very fast," he says.

Chlorogen's system offers two safety advantages. First, because tobacco is not a food crop, there is no risk of modified plants entering the food chain. Also, in CTT, the genes are only inherited maternally and therefore are not present in the pollen that can spread to neighboring fields.

The main disadvantage to using tobacco plants is that unlike corn, rice, or soybean grain, fresh tobacco leaves cannot be stored easily. Chlorogen is studying a proprietary technique to resolve this problem. In the meantime, it has set up mobile extraction units adjacent to the fields to convert the leaves into liquid form immediately after harvesting so that the liquid can be shipped quickly for downstream processing.

Under the agreement, Chlorogen will insert the genes, grow the plants, and harvest the biomass, and Sigma-Aldrich will extract, recover, and purify the proteins. Duncan says that although the downstream process is still in development, he expects it to comprise typical purification and filtration techniques.

So far, the only known disadvantage to the chloroplast method is that it cannot produce proteins requiring glycosylation.

The agreement calls for the production of four specific (undisclosed) proteins that will be sold as reagents and for use in cell culture media. The companies expect to have these proteins commercially available by the end of 2005.

In addition, several of the proteins may be developed for therapeutic applications, including use as blood extenders and blood-clotting agents and for treating amyotrophic lateral sclerosis. Chlorogen also is pursuing a protein for treating ovarian cancer, for which the company hopes to have completed Phase III testing in 2008.

–Laura Bush

WARNING LETTERS

Between 15 September and 15 November, Food and Drug Administration district offices issued two Warning Letters for violations of current good manufacturing practices at pharmaceutical plants.

In late October, the agency's Kansas City district office (Lenexa, KS) warned veterinary pharmaceutical maker Boehringer Ingelheim Vetmedica, Inc. (St. Joseph, MO) to improve its quality systems. Among the failures cited were omissions of certain quality control tests, incomplete process records, inconsistent cleanroom procedures, and certain failures to follow established standard operating procedures.

In September, FDA's New Jersey District office (Parsippany, NJ) cited Guardian Drug Co. (Dayton, NJ)—a contract manufacturer of private-label over-the-counter remedies—for departures from approved procedure and lapses of quality control.

The cited violations included failure to identify particulates found in one batch of simethicone from an outside supplier or investigate whether the particles had found their way into the finished product.

A Guardian spokesman notes that the particles in the simethicone were observed at a third-party site, and only after scraping the bottom of the drum. This material was rejected at the third party's site. Simethicone from the same lot (but different drums) used by Guardian did not contain black particles, and no particles appeared in finished products. The incident occurred during the FDA inspection, and the company completed its investigation after the inspectors left.

Inspectors also cited Guardian for continuing to use industrial-grade adipic acid in OTC products from 2000 through early 2004, and then, after learning of the problem, releasing and shipping products already manufactured using the sub-specification materials.

Guardian responds that its long-time supplier of adipic acid (an inactive ingredient used as a flavor enhancer at the 1% level) had, without informing Guardian, changed its own supplier, moving to a manufacturer that did not qualify its adipic acid as food grade. Immediately upon recognizing the problem, Guardian qualified a new food-grade adipic acid supplier. The company also quarantined the raw material in question and the already manufactured lots. Only after analysis showed that the raw material and quarantined lots in fact met specifications did Guardian release the final product.

Guardian has, a spokesman says, responded to all points raised in the Warning Letter and taken appropriate corrective action.

FDA posts Warning Letters at http://www.fda.gov/foi/warning.htm.

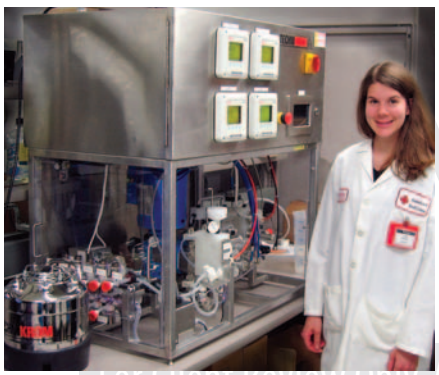
–Douglas McCormick

PROCESS ANALYTICAL TECHNOLOGY

PAT Blending System Helps Control Mobile-Phase Variation

TechniKrom, Inc. (Evanston, IL, www.technikrom.com) has integrated its process analytical technology (PAT) controlled-blending module into benchtop bioprocess and high-performance liquid chromatography systems. Designed for small-scale purification, the systems provide real-time analysis and control of the blended mobile phase for improved reproducibility and accuracy.

Using the company's "Adaptive PAT," the systems eliminate the inconsistencies that result from typical processes performed with variable blends of stock in the mobile phase. "If companies want to prepare and deliver 30% ethanol as the mobile phase, for example, they can end up with anywhere from 25 to 35% ethanol," explains Lou Bellafiore, president and CSO of TechniKrom. Because chromatography separations can be sensitive to just a tenth of a percentage difference in mobile-phase makeup, the variations of feedstocks and mechanical blending are responsible for inconsistent product quality, purity, and yield. "What this means is that you're paying a high cost for not controlling mobile-phase makeup, which is a critical process parameter (CPP)," says Bellafiore.



TechniKrom's benchtop systems for HPLC.

To eliminate mobile-phase variation, TechniKrom's systems measure and correct the makeup of the blend before it's used in the process. "We're not just measuring product in-line after the column purification step. We're using real-time measurements of CPPs to adaptively correct the process stream before it contacts the product," says Bellafiore. This point-of-use control provides both adaptive correction of feedstocks and adaptive control of mobile-phase blending. "If users prepare and connect a tank of 'nominal' 30% ethanol, but it's really 35%, our system corrects it to precisely 30% (±0.1%)," he notes.

In addition, systems not only correct the proportion of feed in the blend but also sense when an incorrect ingredient is used. "If someone connects the wrong feed to the systems—such as accidentally switching the ethanol and water feed lines—it will stop the process, preventing the catastrophic loss of product," Bellafiore points out. The equipment also permits gradient blending with the same control.

Because the technology produces a more consistent mobile phase, the pilot-scale equipment has implications for process development. Researchers testing how a separation behaves with a 5-degree temperature increase, for example, typically work on a "moving carpet" because their results can change with mobile phase variation. Says Bellafiore, "The ability to develop methods is enhanced because you can maintain the mobile phase makeup with extreme precision, which means you can really see the effect of changing process parameters."

According to the company, the Food and Drug Administration has responded favorably to the equipment's adaptive implementation of PAT. FDA will support pharmaceutical companies that make the transition to use such technologies as part of the "Pharmaceutical CGMPs for the Twenty-First Century" initiative.

–Kaylynn Chiarello

REGULATORY

FDA and MHRA Initiate Reforms

Following recent turmoil over their handling of safety concerns regarding antidepressants and pain relievers, the Food and Drug Administration and the UK's Medicines and Healthcare Products Regulatory Authority (MHRA) have announced reforms intended to increase drug safety and transparency in pharmaceutical regulation.

FDA's reforms, announced 5 November by Acting FDA Commissioner Dr. Lester M. Crawford, include:

- Sponsoring an Institute of Medicine (IOM) study of the drug safety system, with emphasis on the postmarket phase.
- Implementing a program for adjudicating differences of professional opinion within FDA's Center for Drug Evaluation and Research.
- Filling the currently vacant position of director of the Office of Drug Safety with a nationally recognized drug-safety expert.
- Conducting drug safety and risk management consultations on marketed and investigational products to address, among other questions, whether a particular safety concern alters the risk– benefit balance of a drug.
5. Publishing, by the end of 2004, the final versions of three risk-management guidances, including the "Premarketing Guidance," "RiskMAP Guidance," and "Pharmacovigilance Guidance."

A week later, in London, Lord Warner, the UK Health Minister, announced a series of reforms to MHRA, including:

- Tightening conflict-of-interest rules for the MHRA's Medicines Commission.
- A new structure for the Medicines Commission ensuring that two lay representatives will sit on the committee, as well as patient representatives on every expert advisory group.
- A renewed demand for pharmaceutical companies to act on their agreement to publish clinical trial data.

–Laura Bush