

## CDER Forms Up Pharmaceutical Inspectorate

**A**s another step along the road to implementation of its Risk-based approach to cGMP regulation, FDA's Center for Drug Evaluation and Research (CDER) is forming a new, uniquely-focused group of specialists to



Janet Woodcock

conduct inspections of pharmaceutical manufacturing facilities. The new "Pharmaceutical Inspectorate" will be staffed by inspectors, specifically trained and experienced in evaluating pharmaceutical manufacturing facilities and processes.

Says Janet Woodcock MD, CDER Director, the move reflects an overall shift in the Center's orientation. "We're moving into a phase of trying to lead and facilitate innovation. It's important for the FDA to be pro-active in all spheres, and one of these is making sure

that drug manufacturing is as efficient as possible."

Until now, FDA field inspectors have been largely generalists, responsible for a wide range of facility types such as food, drugs, chemicals, etc. That's now changing, however, says Woodcock. "Today, the use of increasingly-advanced technology in pharmaceutical manufacturing processes requires specialized knowledge and skills." Members of the Pharmaceutical Inspectorate team will focus almost exclusively on inspecting pharmaceutical manufacturing facilities.

According to Woodcock, the overall goal of the initiative is to introduce greater "application of judgement" into the inspection process "which means more science and risk-based thinking." However, recognizing that FDA can't expect to train the entire field inspection force to this level, CDER has instead opted to develop a cadre of specially trained experts. "We'll have a group of field personnel that will be

trained together with Center people -- as a result of this close working relationship, they'll be on the same page as far as requirements and standards."

CDER plans to have the inspectorate program in place and operational by the end of this calendar year. Woodcock says the group will initially be small (around ten people), but expects to gradually add new personnel. "There are certainly already some highly qualified people in the field offices, but we will also be recruiting for other individuals."

As pointed out by Woodcock, unlike standards development work -- a multidisciplinary activity requiring experts in engineering, facility design and management, pharmaceutical development, chemistry, etc., -- for inspection purposes, FDA won't be looking for a specific kind of expertise. Therefore, although all the inspectors will have a significant level of scientific training, they won't necessarily be experts in any particular discipline. "Rather, we will need people capable of efficiently inspecting a wide range of things when they go into a pharmaceutical plant."

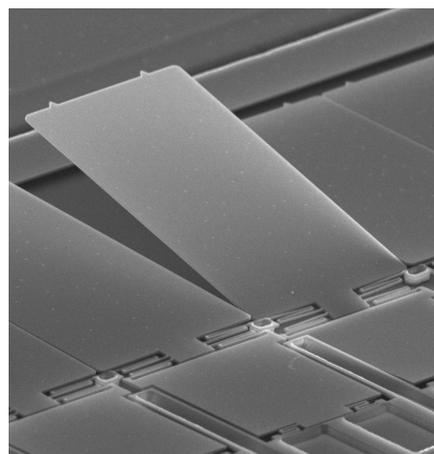
*John Haystead*

## New Consortium Offers Nanotechnology Expertise

Defined as the process of manipulating materials on an atomic or molecular scale, nanotechnology opens the door to a world of pharmaceutical discovery and drug delivery possibilities. The growing interest in nanotechnology has spurred significant investment in R&D and equipment suitable to the development of this progressive technology. Responding to the need to convert nanotechnology to profitable commercial applications are organizations such as the New Jersey Nanotechnology Consortium (NJNC), which aims to support the

entire industry through education, research, and commercialization.

Based at the former Bell Labs nanofabrication facility in Murray Hill, New Jersey, the consortium boasts a membership comprising corporate, government, and academic experts. As explained by CEO, Larry Thompson, NJNC's focus is in developing manufacturable processes for volume fabrication of commercial nanotechnology devices. "We serve as an interface for the pharmaceutical companies, giving them the ability to design and deliver commercial



A MEMS optical switch with submicron-wide springs. The device can be used in integrated RF technology, small features in stents, minimally invasive surgical tools, and in "lab-on-a-chip" devices.



NJNC cleanroom.

devices less expensively than developing their own capability.”

Currently, the Consortium is assisting clients with several nanotechnology projects such as a probe, less than 1mm square, with several hundred “sensors,” that can detect ion flow in the neurological system of laboratory animals. The initial version of the probe will be direct wired but future generations will operate remotely. Also in development are blood pressure monitors that can be inserted into an aorta and remotely

transmit blood pressure to a computer. Concurrently, the NJNC is responding to the need for devices that require features of less than 100nm for real-time detection of chemicals in the blood through nano-patterning and fabrication capabilities.

NJNC’s Nanofabrication facility is the only sub-micron, 200mm wafer fabrication lab dedicated to nanotechnology in the United States. It contains 16,400 sq ft of class 100/10 cleanroom space and houses equipment valued at more than

\$400 million, including one of the world’s few electron-beam lithography nanotechnology tools. A full staff of scientists, researchers, and process development engineers is available on-site. The Consortium’s nanotechnology research capabilities include end-to-end device fabrication using micro electro-mechanical systems (MEMS), nanopositioning systems, optical devices, nanofluidics, molecular probes, DNA fractionation, and cell sorters.

Device prototyping services include design, process development and integration, and testing—all of which are exhibited through a portfolio of nanotechnology devices fabricated using NJNC processes. Thompson notes, “depending on the client’s product, the degree of difficulty in developing a manufacturable process can vary quite a bit. We do have ‘stock-block’ processes that enable us to design a device with the recipes we already possess, or we can design a completely new process to satisfy the client’s need.” Clients are provided with thorough testing to ensure the fabrication of what Thompson defines as “perfectly reliable, essentially fool-proof prototypes”.

*Felicia Pride*



## Vascular sealant spans medical-device/drug-delivery divide

FDA approval, in February, of a new, premixed vascular sealant was more than just good business news for its Canadian manufacturer, Angiotech Pharmaceuticals Inc. (Vancouver, British Columbia), it also marked a milestone in the company’s efforts to develop the sealant into a novel drug-delivery mechanism.

The premixed configuration of “CoSeal,” a biocompatible surgical sealant, features simpler preparation (a three-step process rather than the multiple steps required of its predecessor configuration), an extended lifespan after mixing (two hours vs. 45 minutes), and room-temperature storage rather than refrigeration. In addition, “the entity is more stable now,” says Rui Avelar, M.D.,

vice president at Angiotech. “It takes out the user variability.”

CoSeal facilitates healing by rapidly sealing tissue surfaces, suture lines and synthetic grafts. It forms a flexible seal within seconds, which remains intact and withstands arterial pressure. The sealant is used in vascular reconstruction to achieve adjunctive hemostasis by mechanically sealing areas of leakage, and is a latex-free, synthetic, resorbable material.

Dr. Avelar explains that the earlier configuration of CoSeal required users to be fairly aggressive when pushing the plungers to initiate sealant mixing. Too light a touch forcing the plungers through the barrels caused improper mixing at the end of the tube where the material is

aerosolized. "If users weren't aggressive enough with the plungers, the mixture was not as effective as it could be."

But that problem has been eliminated in the just-approved premixed version. "You can be as aggressive or gentle as you like [with the plunger]. The mixture comes out the same," says Avelar.

Because the product is most often prepared at the operating table and administered during keyhole surgery, the simpler preparation of CoSeal complements its sprayable administration. And from Angiotech's perspective, once you're through that keyhole with a vascular sealant, why not add a medication? "You can make any device better by adding biologics," says Avelar, echoing the company philosophy. For example, he says, "the coronary stent got incrementally better by design changes. But it got logarithmically better by adding meds."

Angiotech develops medical device coatings and treatments for chronic inflammatory diseases through reformulation of the proven anticancer drug, paclitaxel. These treatments stem from the company's discovery that paclitaxel also blocks a cellular pathway involved in inflammation. Angiotech's goal is to develop paclitaxel-based treatments for chronic inflammatory diseases. Polymer-based delivery of paclitaxel has shown promise in preclinical and clinical studies for reducing the biological processes leading to restenosis, the



Rui Avelar, MD

growth of neointimal tissue within an artery after angioplasty and stenting.

Dosing is typically a fraction of that used when a treatment is delivered systemically (eg, it's 1/3,000 the dose for paclitaxel on the stent). Regulators, of course, are already familiar with paclitaxel because of its previous approval and use as an anticancer drug. "We minimize regulators' risk and the risk to patients by employing treatments that are already approved," says Avelar. "You pick your indications, pick your drug, consider how to load CoSeal with the drug (given release kinetics) and then match them to the pathophysiology."

The company is developing polymeric formulations and conducting trials for the delivery of paclitaxel as a stent coating for restenosis, as an intravenous (systemic) treatment for rheumatoid arthritis, and for severe psoriasis. Other medical device programs include paclitaxel-loaded surgical implants for the treatment of restenosis associated with vascular surgery.

Angiotech is allied with such device manufacturers as Boston Scientific Corp. The latter recently submitted to the FDA a pre-market approval application for another medication-enhanced

device, the Taxus paclitaxel-eluting coronary stent. The coating on the stent allows for controlled delivery of paclitaxel, which controls platelets, smooth muscle cells and white blood cells, all of which are believed to contribute to restenosis. Boston Scientific acquired co-exclusive rights from Angiotech in 1997 to use paclitaxel, and launched Taxus in February 2003 in Europe and other international markets. It hopes to launch the product in the United States later this year.

In late January 2003, Angiotech acquired biomaterial and biosurgical company Cohesion Technologies Inc., a company that discovers, develops and commercializes resorbable biosurgical products and medical devices, including sealants, hemostats and adhesion prevention barriers. This acquisition combines Angiotech's drug-loading expertise with Cohesion's approved biomaterials, targeting the emerging field of bioactive devices and implants.

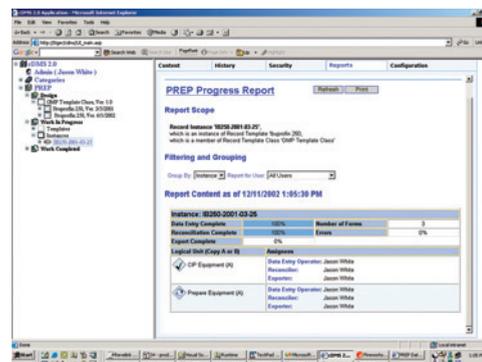
Angiotech uses isolated and dedicated laboratory suites totaling more than 5,000 square feet for research, development, manufacture and testing of pharmaceuticals and pharmaceutical devices. The company announced in late February that it had entered into an interim agreement with Baxter Healthcare Corp. for sales, marketing and distribution of CoSeal as well as a surgical anti-adhesive product called Adhibit.

George Miller

## FDA's 21 CFR Part 11 Draft Guidance Raises Paperless/ Status Quo Issues

In light of FDA's recent Guidance for Industry concerning the scope and application of 21 CFR Part 11, pharmaceutical manufacturing companies may feel less urgency to make the move from a paper-based records management system to a completely electronic one. The draft guidance, which at the moment contains nonbinding recommendations, stated that the administration would heretofore be interpreting the rule more narrowly with fewer records being considered subject to Part 11 compliance.

Although generally considered to be a step in the right direction to facilitate a product's faster time to market, the guidance's immediate implications concerning the pharmaceutical industry has been met with much debate. While some companies that have struggled to comply with Part 11 for the past few years may be breathing a sigh of relief, others may be hesitant to move forward into compliance until the new interpretation has been issued, and still others may be con-



Screen capture of PREP (paper record entry program) that combines Aegis Analytical's data analysis technology with Revelink's document management capabilities.

fused by the new compliance standards altogether.

The new guidance, which is intended to clarify the records that are subject to Part 11, states that Part 11 would apply to companies that “choose to use records in electronic format in place of paper format” and that the “merely incidental” use of computers to generate paper records will not fall under Part 11 requirements. This reinterpretation can be considered par for the course for those companies already pursuing a paperless records management system, but for those that are still maintaining a hybrid paper-based and electronic system, the new guidance may cause uncer-

interpretation to the company. “Companies tend to err on the side of conservatism because they don’t want to fight with FDA. More often than not they want to give FDA what it wants,” Neway says. “When Part 11 came out it was a clear set of guides that a company could feel comfortable applying everywhere. Now companies have to go through this horrendous decision-making process of what is high risk and what is not. It’s a gray zone for companies that are in the process of going electronic.”

Neway predicts that the new guidance may cause companies to implement compliance software less quickly than they would before—a decision that

could affect software development companies such as Aegis, which developed a software system with Revelink, Inc. (Acton, MA) called a paper record entry program (PREP) that can capture paper records and validate the data. “Companies were still struggling to understand the rule, and now that the guidance gives companies a

breather, I think that plans will get pushed off,” Neway explains.

Serge Jonnaert, executive vice-president at American MSI (Moorpark, CA), which developed Celltrack PRO, an enterprise software program that is designed to meet compliance from the beginning of the manufacturing process, is optimistic about the long-term application of the new guidance. Jonnaert believes that FDA’s more risk-based approach to Part 11 should actually encourage companies to move to a paperless management system because the previous interpretation of the rule made electronic compliance seem so overwhelming. “The new guidance at least opens up possibilities for companies to revisit implementing paperless systems,” he says. “A lot of companies until now were in a holding pattern just hoping that something would happen [with Part 11] because they could not face the complexities of implementing

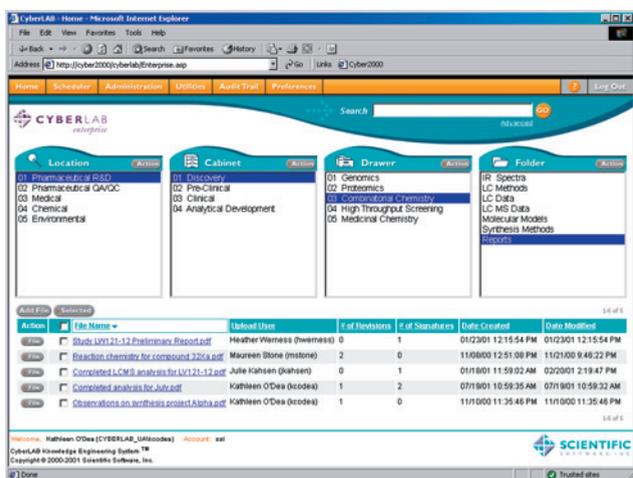
it. I think a lot of companies are stepping it up again.”

AssurX Inc.’s Chief Software Architect Eric June agrees with Jonnaert that the guidance should encourage companies to implement paperless systems. “The draft guidance reconfirms that a risk-based approach is the right way to go as opposed to a hypertechnical approach, which generally stemmed from differing opinions of what an electronic record is,” June says. “FDA has now made it abundantly clear that the term *electronic record* is limited in scope.” This clarified definition of *electronic records* combined with a risk-based approach, June states, should make it easier for companies to decide how to comply with the regulation going forward.

However, June also believes that companies will take some time before moving ahead with their plans to implement electronic records management systems. “In the short term, there will be a pause while companies assess and evaluate the guidance,” June predicts. “But when they come out of that assessment period, they’ll be able to put solutions in place in a much more cost-effective manner.”

Another contributing factor to this hesitation, Jonnaert explains, is that a few years ago companies may have implemented existing production monitoring systems that did not have the architecture to integrate the high security requirements mandated by Part 11, which has made some companies reluctant to try again. “Some vendors claim that they have a compliant solution, but there is just no such thing,” he says. “For the software to provide compliance, one must implement the software correctly, document it with new standard operating procedures, and prove that it is actually being used as it was intended in its intended environment. By themselves, hardware or software cannot be deemed compliant.”

Michael Elliott, vice-president of sales, marketing, and product development at Scientific Software, Inc. (Pleasanton, CA), perceives the new guidance as FDA’s effort to return to the original intent of Part 11, which was to help companies that wanted to move toward paperless systems be more effi-



Screen capture of Scientific Software's CyberLAB electronic document management system.

tainty about which records to validate.

Justin Neway, executive vice-president and chief science officer of Aegis Analytical Corp. (Lafayette, CO), believes that the guidance will have a positive effect on the industry in the long run but may take some time to be completely understood and applied. “FDA is trying to show that it is sensitive to not only their mandate, but also to the practicalities and realities of a changing technology and the fact that science, at the end of the day, should win,” Neway explains. “However, between now and about five years from now, the sorting out process [of the new guidance] is going to be more difficult than people realize.”

Neway states that companies may find the new guidance difficult to implement because it moves the burden of

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cient and to drive productivity gains. “I think FDA is becoming more business friendly. It wants to help American businesses get ahead, and it wants to help human health. The climate is changing from a ‘blocking’ approach to a more helpful approach.” Scientific Software has created the electronic document management system CyberLAB that captures laboratory and documentation data into one system and also acts as a central repository for integration with other document management and statistical systems.

Compliance itself, Elliott believes, shouldn’t be the main impetus for integrating electronic records management systems, but that the business concerns of greater productivity, faster time to market, and increased competitiveness should be the driving factors. “Companies should be looking at how they can improve their business, and then take into consideration the predicate rules and Part 11 as an oversight about how to implement the procedures and practices of a paperless system.”

For companies that may be less eager to implement compliance software as a result of the new guidance, Elliott states that the savings alone from the cost and labor associated with maintaining a paper-based system should be enough to move them toward electronic records management. “If a company takes a step back, it’s taking a step back in terms of its long-term productivity and its long-term competitiveness,” he says. “If you don’t go paperless, you’re going to be left behind.”

*Ronelle Russell*