

FORMULATION/DRUG DELIVERY

Albumin-Bound Nanoparticle Drug Nabs FDA Approval

The US Food and Drug Administration has approved “Abraxane” for injectable suspension (paclitaxel protein-bound particles for injectable suspension) (albumin-bound) as the first protein-bound nanoparticle drug. The collaborative project of American Pharmaceutical Partners, Inc. (APP, www.appdrugs.com) and American Bioscience Inc. (ABI), Abraxane consists of albumin-bound paclitaxel nanoparticles for treating metastatic breast cancer after combination chemotherapy failure or relapse within 6 months of adjuvant chemotherapy.

Abraxis Oncology (the proprietary division of APP, www.abraxisoncology.com) explains that the key to successful delivery of the paclitaxel particles is ABI’s patented (2003) nanoparticle albumin-bound (“nab”) technology, which binds water-insoluble compounds with albumin, a ubiquitous protein in the human body and a natural carrier of hydrophobic compounds, in a nanoparticle state. Tumors are known to naturally “feed” by taking in and retaining albumin-bound nutrients. With the “nab” technology, chemotherapeutic drug molecules enclosed within albumin may be delivered through albumin-activated gp60 receptors, which are used by tumors for taking in these nutrients. The albumin-activated gp60 pathway, activated when albumin binds to gp60 receptors, involves activation of the caveolae-1 protein during the “clustering” process (*i.e.*, the grouping of receptors upon albumin binding). This activation results in the formation of caveolae (or “caves”), which entrap the gp60 receptors attached to the albumin complexes. Substances then are moved out of the bloodstream, across vessel walls, and into surrounding tissues. Because tumor tissues have a greater concentration of blood vessels than healthy tissues, scientists believe there is a greater opportunity

for albumin-bound drugs to reach tumors versus healthy tissues. A novel manufacturing process retains the full biological properties of albumin and helps to increase the bioavailability of the administered drug product.

In contrast to current taxane-based chemotherapies such as Taxol (Bristol-Meyers Squibb Co.), Abraxane doesn’t require the use of toxic solvents such as Cremophor-EL (BASF), which reportedly has been associated with some life-threatening reactions. Abraxane administration also does not require premedication such as the three-day steroid treatment required before the administration of current com-

monly used taxanes. Such steroids also have been associated with adverse effects. Moreover, according to reported results, the absence of solvents enables a higher dose (up to 50%, according to APP/ABI announcements) of chemotherapy compared with solvent-based treatments. APP is scheduled to launch Abraxane on 8 February 2005.

According to the American Cancer society, breast cancer is the leading overall cause of death in women between 20 and 59, causing an estimated 40,000 deaths in 2004.

—Maribel Rios

WARNING LETTERS

Chiron Continues; Compounding Crackdown

The US Food and Drug Administration issued six pharmaceutical CGMP warning letters from 7 December 2004 through 7 January 2005. Five of the letters continued the agency’s crackdown on compounding pharmacies (three veterinary, two human) and one extended the review of the Liverpool influenza vaccine plant belonging to Chiron Corp. (Emeryville, CA, www.chiron.com).

FDA’s Center for Biologics Evaluation and Research (CBER, Rockville, MD, www.fda.gov/cber) issued the Chiron warning on 9 December. This letter was the official notice of the much-publicized shortcomings found during the 10–15 October inspection of Chiron’s troubled Evans Vaccines flu vaccine plant (Speke, Liverpool, UK). FDA made the inspection in the wake of the UK Medicines and Healthcare Products Regulatory Agency’s (MHRA’s) 5 October suspension of the plant’s license.

The six-page, eight-point letter specified failures to adequately:

- Detect and investigate production errors. The warning specifically cited levels of microbial contamination (even after fumigation), a “bulk sterility failure” in one lot pool and inadequate investigation of several lots that had exceeded the company’s alert levels for overall numbers of colony forming units.
- Investigate sterility problems when they did occur.
- Provide for consistent identity, strength, quality, and purity; follow procedures to prevent microbial contamination; and establish procedures that would have prevented the contamination (by *Serratia* and other microbes) that prompted MHRA to condemn the operation.
- Monitor environmental conditions in the aseptic processing area.

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- Establish defined areas for aseptic processing operations to prevent contamination or confusion.
- Ensure cleaning and maintenance of process equipment.

The warning also criticized Chiron's process-simulation program, saying that the existing process-simulation media fills covered only the final vial filling, "which is not representative of the entire aseptic process."

Chiron acknowledged the warning in a brief 10 December news release, saying, "Chiron has since responded to many of these observations in the remediation plan the company submitted to the FDA in November, which is currently underway... Chiron has met with the FDA to discuss these observations, and further meetings are scheduled." As for any additional information requested by FDA, the company said, "Chiron intends to cooperate fully with the FDA in response to the warning letter."

On 12 January, Chiron CEO Howard Pien told the JP Morgan Healthcare Conference that he expected the MHRA, accompanied by FDA observers, to conduct a new of inspections at the Speke plant.

Although the inspections and remediation effort "may advance toward the restoration of the facility's license, as successive phases of manufacturing pass inspection by the MHRA," (in the words of a statement Chiron issued the day of the conference), according to the *Wall Street Journal*, "Pien said there is 'no basis yet to predict whether or when' the company will be able to resume production of flu vaccines for the US market."

Chiron has not responded to questions asking whether inspections actually have been scheduled.

Compounding crackdown continues

The other FDA warnings cited five large-scale compounding operations, two making human drugs and three making animal medicines.

- On 7 December, FDA's Florida District office issued a seven-page, 12-point warning to Lex, Inc. (Medley, FL). Among other complaints, FDA charged

that the company's human prescription and over-the-counter drug operations lacked a quality control unit, failed to train its workers, didn't quality-test ingredients or finished products before shipping or using them, and neglected to test products for stability or microbial contamination.

- On 9 December, FDA's New Orleans District office warned Lincare, Inc. and Reliant Pharmacy Services, Inc. (associated companies at the same address in Clearwater, FL, www.lincare.com) that its large-scale human-drug compounding operation "is akin to that of

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TABLETING/LABELING

Laser-Marking Technique Improves Tablet Branding

Sherwood Technology (Cheshire, UK, www.sherwoodtech.com) has received a US patent for a tablet-marking method that could offer a new anticounterfeiting solution. The technique combines a color-changing additive and a low-power laser to clearly brand edible pharmaceuticals with trademark symbols, dosage information, or even a bar code.

The "DataLase" additive (in either a dry-powder or wet-solution form) is mixed into a tablet-coating formula and applied to the surface of the tablets. The additive reacts to specific wavelengths of light emitted from low-power CO₂ lasers and transforms from a clear or white color to black. Similar to a pen-on-paper technique, the coating instantly changes color in the pattern the laser has "written" on the tablets. According to the company, product degradation won't occur because the low-power laser only affects the outer coating of the tablet. "The technique only needs a fraction of the energy, so it's not destructive," says Andrew Jackson, applications marketing manager at Sherwood Technology.

The main advantage, says Sherwood, is that the technique is quicker and produces less waste than traditional tablet-marking processes. For example, embossing methods tend to crack or damage tablets and result in a high level of quality failures and rejections. Other ink-spraying techniques require drying-time, which slows down the production line.

"On a pharmaceutical packaging line, it's very undesirable to have such a high level of wastage," says Jackson. The Sherwood technique removes this deficiency and thus, "revenue is consequently enhanced," he notes.

Because of counterfeiting and terrorism concerns, the company believes the US Food and Drug Administration may begin requiring tablet-marking techniques such as this in the future. The laser-color-changing technique can create very precise symbols, and thus, "could be used to make a linear or 2-dimensional barcode on the tablet for encoding information," says Jackson. "The small spot size of the laser beam allows high-quality 'pin-sharp' images to be produced." Conventional nonimpact methods such as inkjets may not be suitable for this application because the spray used to form characters often leaves excess ink on the tablet.

"Aesthetically, this isn't very desirable. But also, if it's a code that needs to be read electronically, you're not going to have the proper clarity," notes Jackson.

Sherwood Technology is in discussion with development partners and potential licensees to make the technology available on the US market within the next few months. The company also is in talks with laser suppliers to create an even lower-power device to marry with their technology.

—Kaylynn Chiarello



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a drug manufacturer.” FDA based its conclusion on the observation that several of the company’s products (e.g., acetylcysteine, budesonide) were produced in “enormous amounts of what are essentially copies of commercially available drugs.” The agency said that this practice “goes well beyond the scope of traditional pharmacy compounding and instead more closely resembles a drug manufacturing operation.” In consequence, the agency argues, these products constitute manufactured drugs, and cannot be distributed interstate without proper process approvals.

During the period, two midwestern district offices cited three veterinary compounding operations, charging that the scale of their operations made them subject to the same regulations as a registered manufacturing facility, observing that they often produced compounds identical or

nearly identical to commercially available products, and citing them for failure to guarantee that drugs known to be harmful would not find their way into food-animal populations:

- On 8 December, FDA’s Dallas District office warned Veterinary Enterprises of Tomorrow, Inc. (VET, Mountain View, OK) that its compounding of veterinary drugs (including nitrofurazone, chloramphenicol palmitate, enrofloxacin, omeprazole, dipyrrone, and others) from bulk active pharmaceutical ingredients constituted manufacturing without proper approvals. The agency expressed concern that VET was itself producing bulk drugs, for distribution and resale through veterinarians, rather than compounding individually to fill specific prescriptions. The warning also voiced concern that VET’s products might produce “unsafe drug residues in edible tissues” if administered to food animals, and that the

company did not warn against such applications of known hazardous drugs such as “nitrofurarone” (*sic*), chloramphenicol, and diethylstilbestrol (DES).

- On 17 December, the same office sent a similar warning to Red River Pharmacy Services, Inc. (Texarkana, TX). The letter cited compounding and distribution of veterinary apomorphine, domperidone, chloramphenicol, and nitrofurazone from bulk active pharmaceutical ingredients, often in formulations identical or nearly identical to commercially available treatments, for distribution through third-party resellers. The Agency again questioned possible use of chloramphenicol and diethylstilbestrol in food animals.
- And on 7 January, the Kansas City District Office (Lenexa, KS) cited Omaha’s Essential Pharmacy Compounding (Omaha, NE, www.kohlls.com) also for mass-producing veterinary drugs from bulk active pharmaceutical ingredients. The warning cited large-scale compounding of altrenogest, amikacin sulfate, dipyrrone, flunixin meglumine, ketoprofen, ivermectin, omeprazole, phenylbutazone, and tripeleminamine hydrochloride, “among many others.”

All six warnings demanded a written replies within 15 working days. As of 26 January, FDA had not posted any replies. The warnings can be viewed online at www.fda.gov/foi/warning.htm.

–Douglas McCormick



USP Receives ISO 17025 Accreditation

The US Pharmacopeia (USP, Rockville, MD, www.usp.org) has received accreditation to the International Organization for Standardization (ISO) 17025 standard for compliance in science laboratories. USP’s ISO 17025 accreditation applies to its research and development laboratory and its reference standards laboratory.

The ISO 17025 accreditation examines the overall technical competency of laboratories. It covers every aspect of laboratory management including sample preparation, analytical testing proficiency, and reports and record keeping. This new accreditation reinforces USP’s commitment to implementing international standards.

–Megyn Bates



BIOTECH PROCESSES

Engineered Oilbodies Produce Vaccines and Adjuvants

Recent problems with the US supply of flu vaccine have increased interest in improving vaccine production methods. SemBioSys Genetics, Inc., (Calgary, Alberta, Canada, www.sembiosys.com) has just patented an rDNA vaccine manufacturing method using plant-seed oilbodies to produce a single structure that contains both a vaccine antigen and an adjuvant.

The US patent (number 6,761,914) covers two approaches for attaching antigens to the surfaces of oilbodies—the natural oil-storage organelles found in the seeds of oil-producing plants such as safflower and sunflower. The oilbody itself is an effective adjuvant. When injected into mice, the antigen-coated oilbodies produced a higher immunological response than either antigen alone or a simple emulsion of oilbodies and antigen.

“It’s really that discovery—that this assembly seems to give a potentiation of the immunological response—that is the basis of this patent,” says Maurice Moloney, PhD, the chief scientific officer and scientific founder of SemBioSys. “If you think about the chemical composition of these oilbodies, they are things that the human body is perfectly used to seeing, such as triglycerides and phospholipids,” he explains. “So what we’re really doing, is introducing a structure that appears to fool the immune system into thinking that a whole organism has gotten in. The particle also happens to be about the same size as most pathogenic bacteria.”

Adjuvants generally are combined with antigens in an emulsion to increase the immune response to vaccines. Moloney says initial studies indicate that the oilbodies show efficacy similar to alum adjuvants (the only type approved by the US Food and Drug Administration for human use) and Freund’s Complete, a more rigorous adjuvant used in veterinary vaccines.

Producing the structures

SemBioSys uses two basic methods to produce the oilbody–antigen structures. In one method, recombinant DNA inserted into

plants is expressed to produce a recombinant protein that binds to oleosin, a protein that naturally occurs on the surface of oilbodies (Figure 1). “The protein basically has two domains,” explains Moloney. “One domain is responsible for ensuring that the protein ends up on the oilbody, and the other domain is the protein of interest.” The company already is using this method on an experimental basis to manufacture recombinant proteins such as insulin and apolipoprotein A, a potential treatment for cardiovascular disease. Those nonvaccine proteins are then cleaved from the oil-

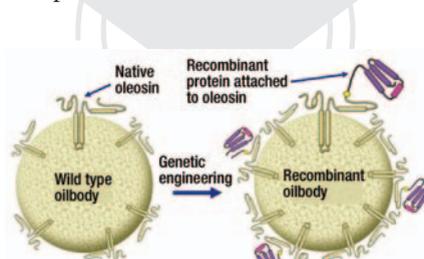


Figure 1: Recombinant DNA inserted into plants is expressed to produce a recombinant protein that binds to oleosin, a protein that naturally occurs on the surface of the plant’s oilbodies.

bodies, harvested *via* centrifugation, and purified using conventional downstream processing.

In some cases, however, the plant will not attach the recombinant proteins to the oilbodies *in vivo*, and they are expressed into the cell cytoplasm instead. The company has developed a method for attaching the proteins to the oilbodies after harvesting. When the cell is disrupted and the cellular compartments are broken up, the targeting sequence on the protein causes it to attach to the oleosin. If necessary, the recombinant protein can be produced in another organism, as long as the protein contains the required targeting sequences.

Easy purification

The nature of the oilbodies simplifies the downstream purification steps. Because the extraction uses a water-based system, the

oilbodies naturally float to the top when centrifuged. “The equipment we use is very similar to what you find in a dairy for removing cream from milk,” notes Moloney. Keeping the oilbodies intact during harvesting does present a challenge, but SemBioSys has already developed a system for doing so with ~90% efficiency.

For the additional purification to remove undesired proteins from the oilbodies, the costly urea-based laboratory systems can be replaced at scale-up with several rounds of washing with inexpensive sodium carbonate and phosphate buffers.

Comparison to other subunit vaccines

SemBioSys’s methods may offer an alternative method for producing subunit vaccines. Although subunit vaccines are more expensive to manufacture than vaccines that contain the whole pathogen, they are desirable because they reduce the likelihood of adverse reactions.

Because plants are grown in the field, plant-based subunit vaccines eliminate the start-up capital costs of fermentation vessels and control systems needed for bacterial- and yeast-based systems. Although the downstream purification of plant systems are more complex, the ease of separating and purifying the oilbodies may keep those costs down. In addition, plant systems may be able to handle certain post-translational protein modifications and folding that neither bacterial or yeast systems can maintain.

The main weakness of using plant systems to produce antigens is speed. It takes 18 months to two years to scale up these production systems, so they are not practical for producing flu vaccines, the strains for which change every year. The company is working on methods for addressing this limitation, however, and plans a new patent filing soon. In the meantime, SemBioSys signed an agreement with Dow AgroSciences in May 2004 to apply its technology for the development of an animal vaccine.

—Laura Bush