



REGULATORY

US Marshals Seize Supplies of GSK Paxil CR, Avandamet

On 4 March, US marshals seized stocks of “Avandamet” (rosiglitazone maleate/metformin hydrochloride, for type 2 diabetes) and “Paxil CR” (paroxetine hydrochloride controlled release, for depression and anxiety) from GlaxoSmith Kline (GSK, Brentford, UK, www.gsk.com) locations in Knoxville, TN, Cidra, PR, and another unspecified location in Puerto Rico.

The marshals acted on warrants obtained by the US Food and Drug Administration. Both drugs are formulated as tablets; FDA complained that longstanding and uncorrected manufacturing problems produced flawed tablets with unreliable amounts of active pharmaceutical ingredients.

In its official statement on the seizures, FDA said that the Paxil CR tablets “could split apart and patients could receive a portion of

the tablets that lacks any active ingredient, or alternatively a portion that contains active ingredient and does not have the intended controlled-release effect.” The agency also found that “some Avandamet tablets did not have an accurate dose of rosiglitazone.”

FDA’s statement advised patients and doctors that, “FDA is not aware of any harm to consumers by the products subject to this seizure and it does not believe that these products pose a significant health hazard to consumers. Consequently, FDA urges patients who use these two drugs to continue taking their tablets and to talk with their health care provider about possible alternative products for use until the manufacturing problems have been corrected.”

GSK’s statement on the seizures (which it referred to as a “disruption of supply”) said the action applied to all strengths of Paxil CR and Avandamet, and noted that, “The company is working with the FDA to resolve these issues as quickly as possible.”

A company spokesman noted that Paxil CR is a two-layer formulation, with active ingredient in one layer and controlled-release components in the other. The company declined to comment on possible causes of the manufacturing problems while the matter is still under investigation.

A review of FDA warning letters published since 2000 failed to turn up any previous CGMP citations for either product. At deadline, FDA had not responded to requests for earlier warning documents, nor to requests for information on observations made on inspection reports.

—Douglas McCormick

WARNING LETTERS

DanChem Technologies and Medsep

The US Food and Drug Administration released drug-product warning letters sent to DanChem Technologies (Danville, VA, www.danchem.com) and Medsep Corp. (Covina, CA).

On 3 March, FDA’s Baltimore (MD, www.fda.gov/foi/warning_letters/) district office sent a three-page letter to DanChem, an active-pharmaceutical-ingredient maker. The letter cited “physical filth” contamination found by a customer in several lots of calcium polycarbophil. The warning also cited “significant violations of current good manufacturing practice” found during agency inspections last fall, including:

- blending out-of-specification calcium polycarbophil with in-spec batches to bring the combined batches within specification; and
- maintaining inaccurate disposal records by labeling, disposing of, and recording debris-filled containers as rejected API.

In response to inquiry, DanChem Technologies stated, “We believe we have taken steps that substantially correct these items and that the additional information we will provide to the FDA will assure them of our ability to continue to produce APIs in compliance with [federal regulations].”

On 15 February the Los Angeles District Office (Irvine, CA) sent a letter to Medsep (a subsidiary of Pall Corp., East Hills, NY, www.pall.com), citing deficiencies in its “Anticoagulant Citrate Phosphosphate Double Dextrose Solution with AS-3 Nuhicel Additive System” (used in blood collection bags manufactured at the same facility).

“Pall responded to a warning letter and is working closely with FDA to ensure the matter is being effectively addressed,” stated Pat Iannucci, vice-president of communications at Pall Corp.

—Douglas McCormick

REGULATORY

UK MHRA Okays Chiron Flu Vaccine Plant; FDA Approval Still to Come

The UK Medicines and Healthcare Products Regulatory Agency (MHRA) last month reinstated Chiron’s license to manufacture trivalent influenza vaccine (tradenamed Fluvirin) at its Evans Vaccines Plant (Speke, Liverpool, UK).

In an official statement, the agency said, “MHRA inspectors have concluded that satisfactory progress has been made in the manufacturing areas which had previously caused concern. Their findings were considered at the MHRA’s Inspections Action Group (IAG) on 1 March 2005, and the IAG’s recommendation to lift the suspension was accepted

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GMPs

Shortages of Key Drugs

The chemotherapy drug methotrexate (injection) in 1-g vials is the most recent entry on the ten-product FDA Current Drug Shortages List. The US Food and Drug Administration listed the product on 18 February, citing unspecified manufacturing delays at Mayne Pharma (Paramus, NJ, www.us.maynepharma.com) and American Pharmaceutical Partners (APP, Schaumburg, IL, www.appdrugs.com).

Overall, the FDA list attributes 77% of the shortages to manufacturing issues, including plant capacity restrictions, with the remaining 23% caused by supply interruptions. The figures continue to grab public attention even as the *Wall Street Journal* headlined the recent shortages of methotrexate and highlighted what the agency has called an increase in the number of medically significant medicines in short supply. (Amy Dockser Marcus, "Critical Cancer Drug Faces Shortage," *Wall Street Journal*, 15 March 2005, p. D1.)

Another methotrexate formulation—made by Mayne, APP, and Bedford Laboratories (Bedford, OH, www.bedfordlabs.com)—had already joined the shortage list last December. The American Society of Health-System Pharmacists' (ASHSP, Bethesda, MD, www.ashp.org) index of

"Drug Products with Limited Availability" cites "manufacturing delays" at all three manufacturers, which have put current requests for the product on back-order.

The other recent entry on the FDA list—Wyeth's "Trecator SC" (ethionamide 250-mg tablets), listed 28 January—is the only solid oral formulation said to be in short supply. The tuberculosis treatment is scarce because of unspecified manufacturing issues; FDA indicates that normal distribution should resume this month.

According to ASHSP, "For unknown reasons, Wyeth has limited supplies of ethionamide tablets (NDC 00008.4130.01). The product is short-dated and expires July 2005. The company is allocating a single 100-count bottle per patient, for use in patients currently receiving ethionamide or for patients initiating therapy. Product is available by drop shipment to wholesalers or by direct order through Wyeth Customer Service (800.666.7248). When ordering ethionamide, the purchasing agent must specify the number of patients being treated and the date each patient started therapy. The company will not estimate a release date."

—Douglas McCormick

FDA drug shortage list by date posted or updated.

Product	Admin.	Posted/updated	Maker	Reason
Methotrexate (1-g vials)	Injection	18 Feb. 2005	Mayne Pharma	Manufacturing issues
Trecator SC (ethionamide, 250 mg)	Tablet	28 Jan. 2005	Wyeth	Manufacturing issues
Methotrexate with preservative (25 mg/mL/2 mL vials)	Injection	15 Dec. 2004	APP	Manufacturing issues
Merrem i.v. (meropenem)	Injection	30 Sept. 2004	AstraZeneca	Supply issues
Celestone Soluspan (betamethasone Injection)	Injection	16 Sept. 2004	Schering-Plough	Manufacturing issues
Pre-Pen (benzyl-penicilloyl polylysine)	Injection	19 July 2004	Hollister-Stier	Manufacturing issues
Avonex (interferon beta 1a)	Injection	5 May 2004	Biogen Idec	Manufacturing issues
Penicillin G potassium and Penicillin G sodium	Injection	6 April 2004	Sandoz and Baxter have product available	Supply issues
Solu-Cortef (hydrocortisone sodium succinate)	Injection	30 Jan. 2004	Pharmacia	Manufacturing issues
Cytovene (ganciclovir)	Powder for Injection	10 Jan. 2003	Roche	Manufacturing issues



MANUFACTURING

Nanoparticle Synthesis Process Facilitates Chiral Separations

Researchers at the Institute of Bioengineering and Nanotechnology (IBN, Nanos, Singapore, www.ibn.a-star.edu.sg) have developed a fluorocarbon-mediated synthesis technique to control the size and shape of nanoparticles for use in pharmaceutical synthesis and chiral separation applications.

The particles, called "IBN-1" and IBN-5," are made with a wet-chemical technique that incorporates two types of surfactants: One is used as a pattern to create a mesoporous structure and the other limits the particle growth to the nanometer scale. According to IBN, the technique produces 50–200-nm nanometer particles with tunable pore sizes ranging from 5 to 30 nm. Says Yu Han, IBN research fellow, "No general method for creating porous nanoparticles has been reported prior to this work."

Previous attempts to produce nanometer-scale particles with nanometer-sized pores were limited in the type of structure, degree of structural ordering, and range of pore size.

One application for the porous nanoparticles is for the production of pure chiral drugs. Typically, liquid catalysts are used to selectively synthesize the preferred chiral molecule, but they are difficult to separate and reuse. The IBN technique can make the catalysts in a solid form, thus enabling them to be filtered out with simple filtering and centrifuging techniques. "Using IBN's porous nanoparticles, the pharmaceutical synthesis can be made much more efficient, while retaining the enantiomeric purity of the products," notes Han. "Compared with traditional catalysts, porous nanoparticles would pro-

vide greater pore accessibility and facilitate molecular diffusion, which are very important for improving the catalytic activity of the process."

Additional applications for the nanoparticles include carriers for drugs, genes, and proteins for biomedical applications. "IBN's porous nanoparticles can act as the host matrix for the synthesis of quantum dots and magnetic nanoparticles in functional materials and bioimaging applications," says Han.

IBN is in talks with several pharmaceutical companies to commercialize the technology, and hopes it will be on the market within the next two years. A US patent application has been filed.

—*Kaylynn Chiarello*

ADVANSTAR
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FORMULATION

Big Pharma Companies Team Up to Develop Once-Daily, Triple-Combination HIV Drug

Gilead Sciences Inc. (Foster City, CA, www.gilead.com) and Bristol-Myers Squibb Company (New York, NY, www.bms.com) have joined forces to bring a three-drug, once-daily treatment regimen for HIV to market. If approved, the treatment would be the first highly active antiretroviral therapy (HAART) for HIV that joins several drugs in a one-a-day tablet. Though HIV is a chronic, long-term treatable disease, pill burden and convenience have been a major challenge. Many HIV treatments require several pills to be taken several times per day, often resulting in missed doses. Says Norbert W. Bischofberger, PhD, executive vice-president of research and development at Gilead Sciences, "To come up with one pill that is essentially a triple-combination regimen is a big plus for patients. It makes the treatment much more convenient."

The new drug will combine Bristol-Myers Squibb's "Sustiva" (efavirenz) and Gilead's "Truvada" (emtricitabine and tenofovir disoproxil fumarate). Because all three drugs are on the market and proven safe for use, the main challenges will be formulation-related such as ensuring bioequivalence and stability for each component and also limiting interactions between the active ingredients.

A key concern for formulators is to develop a tablet that is small enough to swallow. If formulators simply combined the three existing formulations into a trilayer tablet, the drug would be 2.2 g. "You cannot make a pill more than 1.8 g. That's about the biggest size you can go so that people can still swallow it," explains Bischofberger. Limiting the volume and how many excipients are used in the formulations to use could be one way to create a single tablet that is less than 1.8 g.

Gilead and Bristol-Myers Squibb hope to file a new drug application in 2005 and to bring the drug to market in 2006.

—Kaylynn Chiarello

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by the MHRA on the same day. The suspension has therefore been lifted with effect from 5pm on Wednesday 2 March. The company has been informed, and is now free to recommence full manufacturing of the vaccine."

In its own statement, Chiron (Emeryville, CA) noted that, "The decision is conditioned on the understanding that Chiron's high level of commitment to the completion of its remediation plan and ongoing improvements will continue. Chiron will provide the MHRA with regular weekly updates to ensure that progress on its various projects proceeds satisfactorily, and the MHRA may conduct further inspections. Chiron now has clearance to initiate full production of FLUVIRIN vaccine."

The statement also quoted Chiron CEO Howard Pien as saying, "We are grateful for the guidance and effort from the regulatory agencies as we have navigated a path toward remediation. Our employees have worked tirelessly and we are extremely proud of this result. This is a significant accomplishment. In this new beginning we remain focused on continuing to remediate and improve so Chiron can successfully deliver on the results required to supply influenza vaccine for the 2005–2006 season."

The US Food and Drug Administration's Center for Biologics Evaluation and Research responded with a statement of its own. CBER director Jesse Goodman said that, "FDA considers MHRA's action today an extremely important milestone in Chiron's efforts to supply influenza vaccine for the US market for the coming flu season, but work remains. FDA and MHRA will continue to closely monitor Chiron's progress as manufacturing proceeds. When all critical stages of manufacturing are in full swing, and needed corrective actions can be fully evaluated, FDA plans to conduct a comprehensive inspection of Chiron's Liverpool facility to assure that Chiron can produce a safe and effective vaccine."

—Douglas McCormick



FORMULATION

“Stable Liquid” Technology Permits Heptavalent Botulism Vaccine

The US National Institute of Allergy and Infectious Diseases (NIAID, Bethesda, MD, www.niaid.nih.gov) has awarded a \$5.4-million grant to the DynPort Vaccine Company LLC (DVC, Frederick, MD, www.dynport.com) to develop a new heptavalent vaccine against botulism. The vaccine will be stabilized using stable liquid technology owned by Cambridge Biostability Ltd. (CBL, Cambridge, UK, www.biostability.com). The new vaccine will be stable at room temperature, unlike current botulism vaccines. It is being developed as a bioterrorism deterrent.

Botulism is caused by any of seven different serotypes of botulinum neurotoxin produced by the anaerobic bacterium *Clostridium botulinum* and other closely related bacterial species. Because the seven

serotypes have no cross-reactivity, botulism vaccination currently requires administering seven different vaccines, all of which require booster shots to maintain sufficient immunity.

The reason the serotypes have not yet been combined into a single vaccine is that the botulism antigens must be maintained in solutions with tightly controlled pH levels; if the pH level is altered, the antigens are destroyed. Each of the seven antigens requires a different buffer, making it impossible to combine them into a single solution.

By suspending separate dry microspheres in a stable liquid, however, CBL believes it can combine antigens of the seven serotypes in a single vaccine. The method is based on a natural phenomenon, anhydrobiosis. Some organisms are able to sur-

vive in a dried-up form for extended periods. Water within these cells contains a sugar solution that thickens and solidifies into a glass as the organism dries out. Cells are kept in a state of suspended animation until rehydration occurs, and the organism returns to life.

CBL is applying this process to vaccines. A stabilizing sugar is added to the active ingredient of the vaccine. The mix is then spray-dried to form microspheres in which the vaccine is fully encapsulated. The microspheres are then suspended in a stable liquid. Because the ingredients are microencapsulated, they do not react with each other. Upon administration, the sugar encapsulation dissolves in bodily fluids and the antigens provoke an immune response.

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CBL currently uses perfluorocarbons as stable liquids. The US Food and Drug Administration has already approved these compounds for various medical uses, including in ophthalmic surgery and to irrigate the lungs of premature babies. Perfluorocarbons are completely inert—nonhydrophobic and nonhydrophilic—and highly stable. In the body, they evaporate from the blood, diffuse into the lungs, and are then exhaled. The main disadvantage of perfluorocarbons is that because they are so stable, the exhaled gas will collect in the upper atmosphere and contribute to global warming. For this reason, the company is also investigating other inert but less-stable liquids.

The other key to CBL's technology is ensuring the microspheres float in the liquids with neutral buoyancy, explains Howard Smith, research and development manager at CBL. "If the powders were too light, they would just rise to the top of the syringe, and you'd end up injecting only the liquid and no powder," Smith continues. "And if the powders were too dense and sat at the bottom, they would probably block the needle." To achieve even powder distribution in the liquid, CBL adds various inert chemicals to the powder mix to increase the formulation's density. "We adjust the ratio of the chemicals in the formulation to match the density of the stable liquid," Smith says.

Because the stable liquid formulations are anhydrous, they are inherently bacteriostatic, because bacteria require water to multiply. This eliminates the need for preservatives such as thimerosal. It also means the new vaccine is expected to be stable at room temperature, eliminating the need for costly cold-chain storage and distribution. "In general, we are aiming at stability at 55 °C for up to six months," says Smith, "which is as hot as it's ever going to get anywhere."

In addition to offering a cost savings, room-temperature storage would also allow stockpiles of the vaccine to be stored

in multiple locations in large quantities, making mass vaccinations in the event of a bioterrorist attack feasible. It would also permit easy distribution to remote areas.

CBL is now in the process of stabilizing the first of the seven serotypes of the vaccine antigens, the intellectual property of which belongs to the US Army Medical Research Institute of Infectious Diseases. The



In CBL's technique, vaccine antigens (represented by "V" shapes) are enclosed within microspheres, which are then suspended in a stable liquid composed of perfluorocarbons.

company has several products in various stages of development, none of which have gone through clinical trials yet. Smith says the company ultimately wants to work with all 12 of the pediatric vaccines recommended by the World Health Organization, for use in mass vaccination programs in developing countries.

Despite its desire to produce vaccines for the developing world, CBL is a for-profit company. "Generally the large pharmaceutical companies have not been interested in developing markets simply because there isn't enough money to pay for blockbuster drugs," notes Smith. "We're very much going for the Wal-Mart approach, where we have large volumes with small profit margins. If you're selling over a 100 million doses a year, then you've got a shot to make some money."

—Laura Bush

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