Trends-in-Medicine

Quick Takes

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…Highlights from this week's news affecting drugs and devices in development…

SHORT TAKES

- **BOSTON SCIENTIFIC** will collaborate with imaging makers Philips and Siemens in a deal that will combine interventional X-ray systems made by the companies with Boston's iLab ultrasound imaging system.
- **CLINICAL DATA's vilazodone –** The FDA accepted a regulatory application for this experimental antidepressant, entitling Merck, the developer, to a $15.6 million payment from Clinical Data.
- **EDWARDS LIFESCIENCES' Sapien** pulmonic transcatheter heart valve has received a CE Mark to treat congenital heart disease.
- **GENZYME** agreed to pay $175 million and transfer some manufacturing from its Allston plant to another facility in a consent decree reached with the FDA, ending an FDA investigation of manufacturing violations in Allston that caused shortages of Cerezyme (imiglucerase) for Gaucher disease and Fabrazyme (agalsidase beta) for Fabry disease.

NEWS IN BRIEF

BOEHRINGER INGELHEIM's flibanserin – to be reviewed by an FDA advisory committee

The FDA has scheduled a Reproductive Health Drugs Advisory Committee meeting for June 18, 2010, to review this potential treatment for women with hypoactive sexual desire disorder. In clinical trials including 5,000 women ages 18-50, a 100 mg dose of flibanserin increased the number of satisfying sexual experiences the women reported from 2.7 per month to 4.5 per month. Patients taking placebo reported an increase in satisfying experiences to 3.7 per month.

BOSTON SCIENTIFIC – more ICDs cleared

The beleaguered implantable cardioverter defibrillator (ICD) manufacturer received FDA clearance to resume sales of its Livian and Renewal cardiac resynchronization therapy (CRT) devices as well as its Confient, Prizm, and Vitality ICDs. The devices were recalled in March 2010 after the company failed to get FDA clearance for two manufacturing changes. Boston's Cognis and Teligen devices were cleared for sale in April 2010.

Buprenorphine – tapering unsuccessful for opioid addiction

Results of a study including 653 patients addicted to prescription opioid pain relievers showed that tapering them off the drugs with buprenorphine led to almost universal relapse. The results were presented at the American Psychiatric Association's annual meeting. Researchers reported that patients treated with a month of tapering followed by two months of stabilization were rarely treated successfully.

GENZYME's Lumizyme (alglucosidase alfa) – approved for Pompe disease

The FDA approved Lumizyme for treatment of the late-onset form of Pompe disease, a rare genetic disorder in patients age ≥8 resulting from a gene mutation that causes heart and muscle weakness progressing to respiratory failure and death. Lumizyme is believed to replace the enzyme acid alpha-glucosidase to improve muscle function in these patients. It was approved with a risk evaluation and mitigation strategy (REMS) and will only be available through a restricted distribution system. The drug will also have a boxed warning alerting doctors to the risk of anaphylaxis, severe allergic reactions, and immune-mediated reactions.

GLAXOSMITHKLINE's Avandia (rosiglitazone) – calls for withdrawal mounting

Biomedical ethicist Dr. Ruth Macklin from Albert Einstein College of Medicine, head of the ethics subcommittee of the Advisory Committee to the Director of the Centers for Disease Control and Prevention, sent FDA Commissioner Margaret Hamburg a letter recently calling for a halt to the Avandia TIDE trial. She called the trial "unethical," saying that it "violates principles in every guidance document in research ethics."

GLAXOSMITHKLINE's Alli (orlistat) and ROCHE/GENENTECH's Xenical (orlistat) – labels revised

The FDA has completed a safety review of the 120 mg, prescription Xenical and the 60 mg, over the counter Alli and has approved a revised label for Xenical warning of rare cases of severe liver injury in patients taking the drug for weight loss. The FDA is also adding the warning to the OTC Drug Facts for Alli.

GTx's toremifene – fails in prostate cancer

Results of a Phase III trial in 1,590 men with premalignant prostate lesions showed that there was no significant difference in prostate cancer incidence between 20 mg toremifene and placebo.

HbA_{1c} standardization

A consensus statement published in ***Diabetologia*** detailed the first round of standardizing the way glucose levels are referenced and reported worldwide. The recommendations were based on discussions during an October 2009 meeting of the International Diabetes Federation, which included representatives from the American Diabetes Association, the European Association for the Study of Diabetes (EASD), the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC), and the International Society for Pediatric and Adolescent Diabetes.

The consensus states that the IFCC reference system for HbA_{1c} is the only testing method that can standardize the measurement and that results are to be reported in both SI units (mmol/mol) and the U.S. National Glycohemoglobin Standardization Program (NGSP) standard (%). It strongly urges that conversion tables with both SI and NGSP units be easily accessible to the worldwide diabetes community, including patients, and that journals and other printed materials use both units.

The recommendations are in effect until 2011, when they will be reviewed again.

Health Alliance of Greater Cincinnati – settles $108 million cardiology whistleblower suit

The Health Alliance of Greater Cincinnati and Christ Hospital, a former alliance member, will pay $108 million to settle a whistleblower suit claiming that cardiologists were given kickbacks and incentives involving the use of an outpatient cardiology testing unit called the Heart Station. The U.S. Department of Justice (DOJ) alleged that Christ Hospital limited use of the Heart Station to doctors who referred cardiology patients to the hospital. Furthermore, the suit alleged that cardiologists managing to refer enough patients to Christ Hospital to constitute ≥2% of the hospital's gross annual revenues were given a corresponding amount of time to work at the Heart Station, giving them additional opportunities to bill the patients treated there.

DOJ determined that the arrangement with cardiologists violated the Anti-Kickback Statute, which prohibits financial incentives to doctors in exchange for patient referrals. In addition, because procedures and treatments performed as part

of the illegal arrangement resulted in claims to Medicare and Medicaid, the kickback scheme violated the False Claims Act.

JAVELIN's Dyloject (diclofenac) – withdrawn in U.K.

Therabel Pharma UK, the licensee for Javelin's pain product in the U.K., said it has withdrawn all batches of the drug there because of the presence of white particulate matter in some of the product vials. The companies said they are working with U.K. regulatory bodies to resolve the problem.

JOHNSON & JOHNSON – the news gets worse and worse

1. The FDA reportedly is looking into reports of ≥775 serious side effects from recalled J&J drugs, including 7 deaths. Meanwhile, Sen. Tom Harkin (D-IA) is asking the FDA to further probe the recall to determine how the company cooperated with the recall efforts. Sen. Harkin wants the FDA to answer more than 20 questions on the matter by June 11, 2010. Meanwhile, FDA Deputy Commissioner Dr. Joshua Sharfstein said that seizure, injunction, or criminal penalties are being considered against the company's McNeil Consumer Healthcare division because it violated good manufacturing practices.

   Johnson & Johnson has hired an independent consulting firm to help restructure its manufacturing operations and remedy the problems that triggered the massive recall. The company said it will share an action plan addressing the manufacturing process with the FDA in July 2010.

2. The FDA issued a warning letter to Advanced Sterilization Products, a division of J&J/Ethicon, because it failed to correct and upgrade procedures cited by the FDA during inspections in the summer and fall of 2009. Consumers had complained about Sterrad sterilizers, and the FDA's warning letter said the company's actions are not enough to prevent problems from occurring again.

3. Ultram and Ultracet (tramadol) – **labels being revised.** These opioid pain relievers will carry stronger warnings of increased suicide risk in patients who are also taking tranquilizers or antidepressants or who are prone to addiction. Deaths have also occurred in patients with a history of suicidal thoughts or attempts, emotional disturbance, or tranquilizer misuse.

MEDICIS's Dysport (abobotulinumtoxinA) – successful marketing program extended

Medicis has decided to extend through September 30, 2010, its Dysport marketing program, the Dysport Challenge, which offers patients who try Dysport $75 off their next Dysport treatment – or, if they don't like Dysport, $75 off a treatment with the competitor, Allergan's Botox. Medicis said 91.2% of patients who tried Dysport in this program stayed with Dysport the second time instead of switching to Botox.

MELA SCIENCE's MelaFind – to be reviewed by FDA advisory committee

The FDA's General and Plastic Surgery Devices Advisory Committee will review this skin cancer detection device on August 26, 2010. Mela filed a premarket approval application for the device in 2009, and in March 2010 the FDA said the device was not approvable at that time and asked for additional information. Mela met with the FDA to clarify the information needed and submitted it to the Agency in April 2010.

NEUROCRINE BIOSCIENCES' elagolix – positive gynecologic results

Results of a clinical trial including 137 women randomized to elagolix 150 mg daily for 8 weeks showed that elagolix was significantly better than placebo for reducing pelvic pain associated with endometriosis and pain associated with menstruation. The study also showed that the agent reduced pain during sex.

NOVARTIS's patupilone – development in ovarian cancer discontinued

The company will not seek approval to market patupilone for the treatment of ovarian cancer after a trial in 829 advanced ovarian cancer patients did not show any benefit beyond that of existing treatments. Patupilone will still be tested for treatment of some types of colorectal, lung, and prostate cancer.

NYMOX's NX-1207 – positive 3-year results in BPH

A single, injected, 2.5 mg dose of NX-1207 in 85 patients with benign prostatic hyperplasia (BPH) resulted in half of the patients requiring no additional medical or surgical treatment during a 36-month follow-up period. In addition, NX-1207 patients showed a mean 11.8 point improvement in the BPH symptom score. Only one patient in the control group required no additional BPH treatment during follow-up. NX-1207 is currently in Phase III clinical trials.

RETRACTABLE TECHNOLOGIES – Becton Dickinson infringes safety needle patent

It took more than 10 years, but Retractable Technologies finally prevailed, winning a $5 million judgment against Becton Dickinson in a patent-infringement lawsuit over syringe designs. The judge also issued an injunction prohibiting Becton Dickinson from manufacturing or selling the infringing products, though that injunction doesn't become effective until the appeals process is exhausted, which should take at least a year or longer.

In 1998, Becton Dickinson had 90% of the needle market, effectively shutting out smaller competitors and discouraging

sales of lower-cost/lower-profit safety needles. Some sources at the time were accusing Becton Dickinson of conspiring to keep safety needles out of hospitals, lawsuits were being filed, the Occupational Safety and Health Agency (OSHA) was being pushed to act, and Congressional hearings were being called. At the time, much of the attention appeared to be due to complaints by a small, start-up Texas company – Retractable Technologies – which reportedly tried unsuccessfully to sell its safety needle design to Becton Dickinson and was creating "noise" about safety needles to spur interest in its product and help it build a market for its product.

By early 1999, the furor surrounding safe needles was still going on, and personal injury attorneys were targeting needle manufacturers, particularly Becton Dickinson. Only 10% of needles sold were safety needles, mostly because of their higher cost. California had become the first state to mandate the use of safer needles, other states were considering similar legislation, and OSHA, under political pressure to act, was studying the issue.

ROCHE's Avastin (bevacizumab) – breast cancer indication to be reviewed by FDA advisory committee

The FDA's Oncologic Drugs Advisory Committee will meet on July 20, 2010, to discuss two supplemental Biologics License Applications (sBLAs) for Avastin for the treatment of advanced HER2-negative breast cancer in women who have not had chemotherapy. One sBLA is based on the Phase III AVADO study using Avastin combined with docetaxel and chemotherapy, and the second is based on data from the Phase III RIBBON-1 study that combined Avastin with one of three different chemotherapy regimens.

Avastin is currently approved for use with paclitaxel as first-line treatment of advanced HER2-negative breast cancer.

VERTEX's telaprevir – positive Phase III results in HCV

Results of a Phase III trial showed that 75% of patients with the hepatitis C virus (HCV) treated with 12 weeks of triple therapy – telaprevir combined with standard of care (ribavirin plus pegylated interferon) – achieved a sustained virologic response (SVR) vs. only 44% of patients receiving only standard of care. In the study, patients in both treatment groups received 12 or 36 weeks of standard treatment after the initial 12-week treatment period.

Viral relapse rates were 8.6% among patients taking telaprevir for 12 weeks and 9.5% for those taking it for 8 weeks, vs. 28% among those receiving standard therapy.

In another arm of the trial, 69% of patients who received triple therapy for only 8 weeks followed by 16 weeks or 40 weeks of standard of care achieved SVR. Results from two additional Phase III clinical trials using telaprevir, including one in patients who failed previous treatment, are expected to be released in 3Q10.

Standard HCV treatment is difficult to tolerate, with SVR rates of 40%-50%. In this trial, treatment discontinuation rates due to adverse effects were 6.9% for patients receiving 12 weeks of telaprevir, 7.7% among those taking the drug for 8 weeks, and 3.6% for patients receiving standard treatment.

FDA NEWS

➢ House Democrats aim to expand FDA's drug recall ability

Democratic Congressmen appear anxious to give the FDA the power to recall drugs, according to comments made during a House Oversight Committee hearing on the Johnson & Johnson children's medicines recall. There is legislation pending that would give the FDA mandatory recall power over food as well as easier access to company records and civil monetary penalties and would impose new rules on food safety. However, drugs are not included in the legislation.

Rep. Diane Watson (D-CA) said adding drug coverage to the pending legislation could be accomplished by adding "anything ingested through the mouth" to the current bill. FDA Deputy Commissioner Dr. Sharfstein said that if the FDA had the additional regulatory authority to recall drugs, there could have been a more rapid response and recall of the J&J children's medicines. The FDA told J&J it had concerns about the manufacturing process in February 2010, but the children's products were not recalled until April 30, 2010. During the hearing, Rep. Jackie Speier (D-CA) said, "I think the elephant in the room is that you don't have recall authority."

➢ Proton pump inhibitors – PPI fracture risk warning and labeling change

The FDA issued a warning to consumers and healthcare professionals advising that the use of proton pump inhibitors (PPIs) for ≥1 year – or at high doses – may increase the risk of bone fractures. The labeling on all prescription and over-the-counter proton pump inhibitors will be revised to reflect the increased risk. The warning is a result of an FDA review of several epidemiological studies that reported increased fractures of the hip, wrist, and spine in patients using these agents.

➢ FDA public workshop on unmet device needs

As part of an initiation by the FDA's Center for Devices and Radiological Health (CDRH) to more proactively facilitate medical device innovation, the FDA will hold a public workshop, "Identifying Unmet Public Health Needs and Facilitating Innovation in Medical Device Development" on June 24, 2010.

Workshop participants will be asked to identify:

1. The most important unmet public health needs.
2. Barriers to the development of devices to meet those needs.
3. Actions the federal government can take to remove or minimize such barriers.

The FDA said that the discussion of these topics should not be limited by current statutes or regulations. There will be an open dialogue between the members of the federal Council on Medical Device Innovation (composed of representatives from various agencies, including NIH, CDC, CMS, DOD, and the VA) and experts from the private and public sectors, including industry, academia, patient and consumer advocacy groups, professional organizations, and other state and federal bodies.

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