Trends-in-Medicine

Quick Takes

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

SHORT TAKES

- **BIOFORM MEDICAL/CHEMISCHE FABRIK KREUSSLER's Asclera (polidocanol)** – The FDA approved injectable Asclera to treat spider veins less than 1 mm in diameter and reticular veins that are 1 to 3 mm in diameter.
- **COLLEGIUM PHARMACEUTICAL** filed an Investigational New Drug (IND) application for COL-172, a tamper-resistant, extended-release oral opioid formulation, and COL-003, a tamper-resistant formulation of extended-release oxycodone.
- **COVIDIEN's Ultra-Technekow DTE** and **LANTHEUS's TechneLite** – in short supply. The FDA reported that material sourcing issues have caused a shortage of both of these Technetium Tc99m generators.
- **DEPOMED** filed an NDA to market DM-1796, a once-daily form of gabapentin, for postherpetic neuralgia. Depomed has licensed the compound to Abbott Products, a division of Abbott Laboratories.
- **JOHNSON&JOHNSON/ETHICON** has until June 15, 2010, to consider a buyout offer for its Ethicon breast cancer products unit from Devicor Medical Products, a division of private equity investment firm GTCR Golder Rauner LLC. Financial details were not disclosed, but Ethicon said the offer was "irrevocable and unconditional."

NEWS IN BRIEF

ACRUX's Luramist (testosterone metered dose transdermal spray) – Vivus ends partnership

Vivus announced it will return the rights to Luramist, a women's testosterone treatment, to Acrux subsidiary FemPharm and has ended its development and commercialization partnership. Vivus President Peter Tam issued a statement saying the decision was based on "the significant long-term safety requirements for the approval of testosterone products in women." Instead, Vivus will focus on developing obesity and erectile dysfunction treatments. Luramist was developed to treat hypoactive sexual desire disorder, or low libido, in women. In 2008 Vivus and the FDA agreed upon a Special Protocol Assessment for Phase III efficacy trials for Luramist.

ANTISOMA's vadimezan – Phase III lung cancer trial stopped

Interim results of a Phase III trial of vadimezan in non-small cell lung cancer (NSCLC) showed no significant survival benefit for previously untreated patients compared to chemotherapy alone, causing the trial to be halted. Vadimezan was designed to cause tumor necrosis through damage to tumor vasculature. In the Phase III clinical trial, 1,200 previously untreated NSCLC patients received the agent in combination with chemotherapy for 6 months, but the combination extended survival to only 14.9 months vs. 11 months for chemotherapy alone. A second trial using vadimezan in patients with NSCLC who have failed previous therapies is still underway.

Beta interferons – a way to predict response in MS?

Stanford University researchers have found, in a mouse model, two subtypes of multiple sclerosis (MS), one of which responds to treatment with beta interferons. The research was published last week in ***Nature***. Furthermore, a simple blood test may be able to determine which patients will benefit from beta interferon treatment. Patients with MS driven by interleukin-1 (IL-1) seem to respond, while those with disease driven by IL-17 do not. The research may eventually help determine which patients are most likely to respond to Biogen Idec's Avonex, Merck's Rebif, and Bayer's Betaferon, which together have sales of $6.1 billion.

BLUE CROSS BLUE SHIELD OF DELAWARE (BCBSD) – investigated for denying cardiac imaging coverage

The insurer said it will comply with a request by the Senate Committee on Commerce, Science, and Transportation to supply documentation for all cardiac imaging coverage denials it issued during the past five years. Several hours after the Senate inquiry began, BCBSD said that it had halted all stress test denials. Local news reports had detailed cases of patients who had been denied coverage for nuclear stress tests even though they exhibited common heart disease symptoms that would indicate a stress test is warranted under established guidelines.

BOEHRINGER INGELHEIM – releases Type 2 diabetes survey results

In an effort to understand common obstacles physicians face when treating Type 2 diabetes, Boehringer Ingelheim surveyed 203 family physicians and 100 endocrinologists active in the Sermo online community for physicians. Those polled treat an average of 47 patients with Type 2 diabetes per week and have been in practice an average of 19 years. The key findings were:

- 71% said using an integrated team approach in the early stages of treatment was feasible for their practice, but only 7% said that the majority of their colleagues use an integrated approach.
- 44% said that more than half of their patients develop at least one diabetes complication.
- 94% said kidney health is important to understanding the risk of other complications, but 40% do not believe their newly diagnosed patients know that Type 2 diabetes can lead to kidney disease.
- Patients with Type 2 diabetes continue to have high rates of obesity even though 66% of physicians said they typically refer these patients to a dietitian or nutritionist. 63% said that dietitians and nutritionists were most helpful in assisting with weight loss.
- Lack of motivation, lack of adherence to medication, and inability to lose weight were the most commonly cited reasons physicians said their patients' glucose was not effectively controlled.
- Compliance with lifestyle modifications or medications and patient understanding were the main obstacles to preventing complications.

BOSTON SCIENTIFIC's ICDs – first a recall, now criminal and securities investigations

According to the ***Wall Street Journal***, an internal Boston Scientific memorandum indicates the company received a subpoena from Department of Justice prosecutors and that the Securities and Exchange Commission (SEC) started an informal inquiry into the circumstances surrounding the recent recall of all its implantable cardioverter defibrillators (ICDs) and cardiac resynchronization therapy defibrillators (CRT-Ds). The devices were recalled March 15, 2010, when Boston Scientific notified the FDA that there were two manufacturing changes it had failed to clear with the Agency. Now, government investigators are asking for documents about the discovery that the company had not obtained clearance for the changes and any reports of injuries. In addition, Boston Scientific is being asked for communications with regulators, physicians, and stock analysts about the recall.

The recall applies to all devices in the company's Cognis, Confient, Livian, Prizm, Renewal, Teligen and Vitality product lines. The FDA previously advised that these devices not be implanted until it reviews and approves changes made to them but did not see reason to recommend explants of any of the devices. Boston Scientific also advised that the FDA is not expediting the review of its supplemental filing seeking post facto approval of the changes.

CEPHALON's Nuvigil (armodafinil) – rejected by FDA for jet lag

Cephalon received a complete response letter from the FDA denying approval of Nuvigil, a longer-acting form of Cephalon's Provigil (modafinil), for jet lag treatment. The company said the FDA questioned the "robustness" of patient-reported effect assessments which were used as an efficacy

measure in the last clinical trial. The trial also measured efficacy with a multiple sleep latency test. Cephalon said it will schedule a meeting with the FDA to discuss the issue. Provigil is approved for treatment of sleepiness caused by obstructive sleep apnea, narcolepsy, or shift work disorder.

CT colonoscopy debate – topic of heated FDA public hearing

During an FDA public hearing that was meant to be part of an Agency campaign to improve scanning safety, former FDA scientist Dr. Julian Nichols said he was fired after raising concerns about the risks of routine CT scanning to screen patients for colon cancer. He also said that he and other FDA scientists "were pressured to change their scientific opinion." The FDA replied in a statement that allegations of retaliation against the researchers had been looked into by the FDA Inspector General and that further investigation was not pursued.

Comments during the public hearing illustrated a long-standing charge by scientists that the FDA has ignored radiation safety concerns related to CT scanning, particularly when used for cancer screening. Although the FDA prohibits employees from discussing device manufacturers' applications, the ***New York Times*** reported that internal FDA documents reveal that "Agency managers sought to approve an application by General Electric to allow the use of CT scans for colon cancer screenings over the repeated objections of Agency scientists." The FDA review of the application is still underway.

FDA implementing pediatric device requirement

The FDA announced that it will begin to require that device manufacturers provide premarket application information on pediatric patients with the disease or condition the device is intended to treat. The requirement, in the Food and Drug Administration Amendments Act of 2007, says that manufacturers must provide certain pediatric information, if readily available, with premarket approval application or supplement, humanitarian device exemption requests, or product development protocols. The information must include a description of any pediatric subpopulations the device is intended to treat as well as the number of affected pediatric patients. ***If the manufacturer does not submit such information, the FDA may not approve the application until the required information is provided.***

FDA now considering 3 diet drugs

Orexigen Therapeutics' Contrave (bupropion + naltrexone), which was submitted to the FDA on March 31, 2010, makes the third weight loss drug under review at this time by the FDA. Vivus's Qnexa (phentermine + topiramate) was submitted in December 2009, and an Endocrinologic and Metabolic Drugs Advisory Committee meeting is scheduled for July 15, 2010. Arena's Lorcaserin, a first-in-class selective serotonin 2C receptor agonist, was submitted later in December 2009, but no advisory committee meeting has yet been scheduled, possibly because the company advised the FDA that it was submitting supplemental information.

GenVec's TNFerade – Phase III pancreatic cancer trial discontinued

GenVec announced it is discontinuing Phase III trials of the once promising TNFerade, an adenovector carrying the gene for tumor necrosis factor-alpha (TNF-α) because interim results determined that it was unlikely to extend survival in pancreatic cancer patients vs. standard treatment alone. Earlier trials showed an 8% lower risk of death in advanced pancreatic cancer patients receiving TNFerade combined with standard therapy. In November 2008, TNFerade received a fast track designation from the FDA based on those earlier results. GenVec is also developing vaccines and has a collaboration with Novartis AG for hearing loss treatments, but the company hoped TNFerade would be its flagship product.

H1N1 flu resurgence seen in southeast

The Centers for Disease Control (CDC) are concerned about a resurgence of the pandemic H1N1 flu in southeastern states during the past week. Officials called the increase in cases in Georgia "unusual" and most worrisome. In late March, 40 patients with confirmed H1N1 infection were admitted to Georgia hospitals, and the flu has been more prevalent there than in any other state during the past three weeks, officials said. Georgia also reported one of the lowest vaccination rates in the country, and now the H1N1 virus is affecting mostly adults with underlying conditions, according to the CDC.

Georgia, along with Alabama and South Carolina, are reporting regional H1N1 activity while Arkansas, Louisiana, Mississippi, North Carolina, Tennessee, and Virginia are reporting local flu activity. Outside the southeast, Hawaii, New Mexico, and Puerto Rico have also reported local activity.

Investigating the investigators (FDA)

A March 30, 2010, report in ***Politico.com*** details how two officials at Amphastar Pharmaceuticals paid to have Dr. Janet Woodcock, director of the FDA's Center for Drug Evaluation and Research (CDER), investigated. The private investigators collected ***public*** information on Dr. Woodcock, her husband, two daughters, in-laws, and her travel to Thailand, looking for an improper link to Amphastar's competitor, Momenta.

The investigators also collected information on a second FDA official, Moheb Nasr, PhD, director of the FDA's Office of New Drug Quality Assessment.

Amphastar was concerned about the pace of the FDA review of its application for a generic enoxaparin (Sanofi-Aventis's Lovenox, a low molecular weight heparin) and was worried

the delay was due to an inappropriate relationship between Dr. Woodcock and Momenta. And there was a smoking gun, from Amphastar's perspective – Dr. Woodcock had co-authored a paper with a Momenta official and was a featured speaker with that official at a conference in Thailand in 2007.

Was the use of private investigators improper? Maybe not if you consider this part of the ***Politico.com*** story: "Collusion between FDA officials and drug companies has happened before – a history Amphastar was well aware of when it launched its investigation. In 1989, three FDA officials pleaded guilty to taking bribes and two companies said they had submitted false information to the government in a scandal that rocked the pharmaceutical world. And that scandal came to light only because an aggrieved drug company had hired private investigators to dig into suspicious relationships."

However, Amphastar's investigators found no evidence of any impropriety on the part of Dr. Woodcock or Dr. Nasr. And ***Politico.com*** said that in February 2010 an FDA legal counsel concluded, "Woodcock's interactions with Momenta did not constitute a conflict of interest."

Read more:
www.politico.com/news/stories/0310/35212_Page3.html#ixzz0jlBD3Hqb

JOHNSON & JOHNSON/DEPUY SPINE's Charité – no longer available

J&J confirmed that the Charité artificial lumbar spine disc is no longer in production and has been replaced by the In Motion artificial disc. J&J has been phasing in the In Motion disc since it was introduced in 2007. According to a J&J official, In Motion "builds on the essential sliding core design of the Charité." The Charité disc has been implanted in more than 5,000 U.S. patients since it received FDA approval in 2004, but criticism of the design and methods used to gain approval of the disc, as well as lawsuits filed against the company, have been problematic. In addition, the Centers for Medicare and Medicaid Services (CMS) issued a non-coverage decision for all lumbar total disc devices for patients over age 60 based on difficulties with the Charité disc.

MYRIAD GENETICS – judge nullifies breast and ovarian cancer gene patents

A U.S. District judge has invalidated patents held by Myriad on the BRCA1 and BRCA2 breast and ovarian cancer genes, saying that while isolation of the genes was a "valuable scientific achievement," patents are not warranted because the "isolated DNA is not markedly different from native DNA as it exists in nature." Myriad said it will appeal the decision, a move that would take the case to the 2nd U.S. Circuit Court of Appeals in New York.

The ultimate decision on whether genes can be patented will have far-reaching implications for the biotechnology industry which has maintained that it should hold patents on successfully isolated genes because of the cost of the research involved. However, scientists and rights organizations disagree, arguing that isolated genes are no more than a DNA product inherent in the body that should not be patented.

In 2008 the American Civil Liberties Union and the Public Patent Foundation sued Myriad aiming to force the company to license the BRCA1 and BRCA2 genes so that women who may be at high risk for the mutations have options allowing them to use other companies to assess their genetic risk.

North American Spine Society (NASS) survey – finds 24% of members considering dropping Medicare

If CMS enacts a 21% reimbursement reduction later this year, 24% of 340 spine care physicians surveyed by NASS said they would stop participating in Medicare, and more than a third of them said they would contract with Medicare patients privately instead. NASS President Dr. Ray Baker said the survey results indicate the fear physicians have nationwide and noted that healthcare reform does not address these concerns. Among the specific actions NASS members said they would take are:

- 20.6% would limit the number of Medicare patients they see.
- 14% would reduce time spent with Medicare patients.
- 12.9% would stop providing certain services.
- 11% would begin referring complex cases.

NOVARTIS's Stalevo (entacapone + carbidopa + levodopa) – FDA investigates prostate cancer risk

The FDA will evaluate clinical trial data which suggest that Stalevo, a therapy for Parkinson's disease, increases the risk of developing prostate cancer. This is part of an ongoing safety review, and the FDA has no new conclusions or recommendations about the use of Stalevo but said in a drug safety communication that healthcare professionals "should be aware of this possible risk and follow current guidelines for prostate cancer screening."

The FDA will review data from the long-term STRIDE-PD trial that compared Stalevo to carbidopa + levodopa, which showed that more patients taking Stalevo were found to have prostate cancer. Previous, shorter trials did not show an increased risk of prostate cancer with Stalevo.

Silicone breast implants – new concern with French implants

European plastic surgeons have been warned not to use silicone gel-filled breast implants from Poly Implant Prothèse

(PIP) and to "quarantine" any implants in their possession. Although the European Medicines and Healthcare products Regulatory Agency (MHRA) said that there was no evidence as yet that they could harm patients, both the MHRA and the French medical device regulatory authority, AFSSAPS (Agence Française de Sécurité Sanitaire des Produits de Santé), are investigating the situation.

The ***Telegraph*** in the U.K. quoted Nigel Mercer, consultant plastic surgeon and president of the British Association of Aesthetic Plastic Surgeons, as saying, "Concerned patients should contact their surgeon to find out what implants they have. Only PIP implants are involved and as yet there is no evidence that the gel they contained is harmful and we understand that it will not leak into the body."

There have been no safety questions raised about the lastest silicone implants from U.S. companies – Johnson & Johnson/ Mentor or Allergan. However, the publicity about the PIP implant problems could have a negative impact in the U.S., where many doctors and women are still skittish about the safety of silicone implants.

SANOFI-AVENTIS's Multaq (dronedarone) – U.K. okays use for some AF patients

The National Institute for Health and Clinical Excellence (NICE) has overturned its previous position and now recommends Multaq as a ***second-line*** treatment for patients with atrial fibrillation that cannot be controlled with other medications or who cannot take other medications because of adverse effects. Previously, NICE did not recommend Multaq because of the higher cost vs. warfarin and because it was deemed less effective. The turnaround came after cardiologists and members of parliament wrote to NICE earlier this year, asking that the drug be recommended.

In the last issue of Quick Takes, we omitted this item, but we considered it important enough to add to this issue.

GLAXOSMITHKLINE's Rotarix vaccine – FDA suspends use

On March 22, 2010, FDA Commissioner Dr. Margaret Hamburg asked clinicians to suspend use of GSK's Rotarix rotavirus vaccine and use Merck's RotaTeq vaccine instead. This was a very unusual move because Rotarix was ***not*** being removed from the market; its use was just being suspended for at least 4-6 weeks while the FDA studies the vaccine. The problem with Rotarix is that it is contaminated with PCV1 virus.

Here are some key points relating to this action:

- The FDA says there is no evidence that the PCV1 material in Rotarix is dangerous. PCV1 is not known to cause ***any*** disease in humans or animals (including pigs).
- The FDA believes Rotarix is safe, but it doesn't want it used until this issue is better studied and understood.
- There will be an FDA Advisory Committee meeting on Rotarix within the next 4-6 weeks.
- Other countries may decide to continue to vaccinate with Rotarix because the burden of the disease in those countries may be greater than in the U.S. where it is low.
- The FDA does not know the nature of the contaminant. It doesn't know if the contaminant is DNA fragments or intact virus or whether the virus in the vaccine is able to replicate.
- About 1 million kids in the U.S. have been vaccinated with Rotarix.
- Kids who have received one dose of Rotarix are advised to get 2 doses of RotaTeq instead of one additional dose of Rotarix.
- Parents who are concerned are being advised to call their healthcare provider to determine which vaccine their child received – which could mean doctors will be flooded with calls.
- Kids who have received the vaccine do not need to be monitored any more than usual, in the FDA's opinion. There is no additional surveillance being recommended.
- Suspension instead of withdrawal is a tactic the FDA has used with foods and is now applying to drugs. For example, this approach was used when salmonella was found in pistachios. Dr. Hamburg said, "It is important to have a little more flexibility in our regulatory approach and not just an all or none, proceed with business as usual, or pull it from the market, and that is what we are trying to achieve here." This may be the first time this approach has been applied to drugs, but Dr. Hamburg was not certain of that.
- The PCV1 viral contamination was discovered by an academic research team using PCR to screen for unknowns. Dr. Hamburg said the virus "was identified and reported to the manufacturer, GSK, who began to investigate to see if they could determine if the finding was in fact the case, and then they reported it to us, and then we too began our own internal examination of the product and began working with the company to define some of the critical questions that needed to be addressed."
- The FDA does not know how the PCV1 got into the vaccine, which is manufactured in Europe. ***The FDA does not know if any components of the vaccine come from China***.
- The FDA does not expect Rotarix will be taken off the market in the future.

- Doctors do not have to follow the FDA's recommendation. They could still use Rotarix if they want to – and if they can get it. The FDA's action is "simply a recommendation." However, it seems unlikely parents will want Rotarix used.
- *Will there be a shortage of rotavirus vaccine or can Merck supply the entire market?* There probably will not be a shortage in the short run, but longer term it may be an issue, though there is a National Stockpile that could be drawn down. Dr. Hamburg said, "There is a supply of RotaTeq…It is also available in our National Stockpile. We are working with Merck in terms of trying to assure availability…We don't have reason to believe Rotarix will be coming off the market…and we will be working with both companies as we move forward in our decision making."

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