TRENDS-in-MEDICINE

January 30, 2011

by Lynne Peterson

Quick Takes

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

SHORT TAKES

- **ACTELION and GLAXOSMITHKLINE's almorexant** – The companies halted Phase III development of this dual orexin receptor antagonist for sleep disorders after reviewing data from additional clinical studies, which were conducted to further establish the clinical profile of almorexant, including the tolerability profile. However, the companies aren't giving up on the class; their collaboration on orexin receptor antagonist therapies will continue.
- **Alzheimer's disease** – Research published in ***Nature*** suggests that IGF-II may be a potential therapy for dementia. Researchers reported on a study in rats that found declarative memory (the ability to remember things, places, and facts) can be improved by giving IGF-II. *Watch for some pharma to investigate this further.*
- **AMYLIN PHARMACEUTICALS/LILLY's Bydureon (exenatide extended-release)** – Amylin plans to start a cardiovascular safety trial of this weekly injectable for Type 2 diabetes in February 2011, with results expected in 2H11. The company also is developing a pen injector for Bydureon, expected to be ready by 2012.
- **ANGIODYNAMICS' NanoKnife** – The company got a warning letter from the FDA about its marketing of this surgical system, which is cleared only for soft tissue surgical ablation. The FDA said some of the company's marketing claims have been for off-label uses.
- **BIOGEN IDEC/ELAN's Tysabri (natalizumab)** – Six new cases of progressive multi-focal leukoencephalopathy (PML) were reported in multiple sclerosis (MS) patients, bringing the total to 85. *Remember: The FDA has had a safety review of Tysabri underway for some time, and approval was based on a PML incidence <1:1,000.*
- **BIOSANTE PHARMACEUTICALS'** melanoma vaccine was granted orphan drug status by the FDA.
- **EISAI's eritoran**, an experimental drug to treat severe sepsis, missed the primary end-point, failing to show a mortality benefit vs. placebo, in the Phase III ACCESS trial. Eisai plans to analyze the data from the trial further before deciding whether to discontinue all development.
- **FURIEX PHARMACEUTICALS' MuDelta**, a combination mu-opioid receptor agonist and delta-opioid receptor antagonist for diarrhea-predominant irritable bowel syndrome (IBS-D) that is in Phase II development, was granted fast track status by the FDA.

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- **GLAXOSMITHKLINE's Avodart (dutasteride)** – The FDA declined to expand the approval for this benign prostate hyperplasia drug to include prevention of prostate cancer, following the advice of its advisory committee, which concluded that the risk of aggressive tumors outweighed the benefits.
- **JOHNSON & JOHNSON** said in a court filing that the U.S. Justice Department closed its criminal antitrust investigation relating to its sale of blood reagents. However, J&J's Ortho-Clinical Diagnostics unit and **Immucor**, a competitor, still face civil lawsuits alleging price-fixing.
- **LIGAND PHARMACEUTICALS** acquired **CyDex Pharmaceuticals**, which specializes in reformulating existing drugs. CyDex also has Captisol, a controlled-delivery technology that works by encapsulating the active agent within rings of sugar molecules.
- **Mammography** – A study out of Spain looked at four population-based breast cancer screening programs in that country and found there was no difference in cancer detection between screen-film mammography (SFM) and digital mammography, but the recall rate and false-positive risk were lower with digital mammography.
- **National Association of Chain Drug Stores (NACDS)** launched NACDS Mobile, a new mobile website that serves as a "guide on the go" to NACDS meetings, advocacy, and public relations (**http//m.NACDS.org**). It's designed to work with smartphones and will have meeting/conference news and public policy news.
- **NOVARTIS** is buying laboratory diagnostics services company **Genoptix**, a move designed to speed development of companion diagnostic tests. Genoptix will become part of Novartis Molecular Diagnostics, a unit within the Novartis Pharmaceuticals division.
- **OPTIMER PHARMACEUTICALS' fidaxomicin** was granted priority review by the FDA. The FDA's Anti-Infective Drugs Advisory Committee will review the drug on April 5, 2011, and the PDUFA date is May 30, 2011.
- **PFIZER/KING PHARMACEUTICALS/PAIN THERAPEUTICS' Remoxy (tamper-resistant oxycodone CR)** – The FDA accepted the resubmission of the NDA for this opioid for review. The PDUFA date is June 23, 2011.
- **REGENERON PHARMACEUTICALS/BAYER's aflibercept (VEGF Trap-Eye)** – Positive Phase III top-line results in macular edema were announced in December 2010, and the full data are expected to be presented at the Angiogenesis, Exudation, and Degeneration 2011 conference at Bascom Palmer Eye Institute in Miami on February 12, 2011.
- **ROCHE/GENENTECH's Boniva (ibandronate)** – The FDA told the company a print ad with actress Sally Field "misleadingly" overstated the osteoporosis drug's efficacy. The company agreed to stop using the ad.
- **SINOPHARM GROUP** is buying a stake in units of **Le Ren Tang Pharmaceutical Group Co. (LRT)** to expand in China's northern Hebei province. LRT sells >20,000 Chinese-made pharmaceutical products to >1,000 hospitals across the province.
- **TEVA PHARMACEUTICAL INDUSTRIES** is buying Peru-based **Corporacion Infarmasa**, which makes and sells brand-name and generic drugs, including corticosteroids, antibiotics, and allergy and pain medications.

NEWS IN BRIEF

ABBOTT LABORATORIES

- **Job cuts** – The company is eliminating 1,900 employees, mostly in U.S. marketing and manufacturing positions.
- **RX Acculink** – The FDA's Circulatory System Devices Advisory Committee recommended expanded approval for these carotid stents, voting 7-3 (with 1 abstention) that the FDA should allow their use in patients who are not at high risk for complications from carotid endarterectomy. A final FDA decision is expected in 2H11.

AMGEN

- **Is buying BioVex**, which is developing a melanoma vaccine, OncoVEX.
- **Raised prices on several medications** to offset falling revenue from anemia drug Aranesp (darbepoetin), which is being hurt by Medicare bundling in dialysis.

Angiotensin receptor blockers (ARBs) – try an ACE first

A paper published in the ***Canadian Medical Association Journal*** suggests that restricting prescriptions for ARBs to patients who are intolerant to ACE inhibitors could save millions of dollars in healthcare costs without any adverse effects on cardiovascular health. The authors said one Canadian province already restricts ARB use this way and estimated that if all Canadian provinces had followed suit, they would have saved more than C$77 million in 2005-2006 alone.

ASTRAZENECA's Brilinta (ticagrelor) – company answers FDA, but is the answer enough?

In December 2010 the FDA asked AstraZeneca for further analysis on the pivotal PLATO trial, and AstraZeneca said it responded recently, saying that the likely reason there was less effectiveness in North American patients than European patients was most likely due to differences in aspirin use. The company floated that explanation at the advisory committee meeting, so it is not clear whether the FDA will accept it now or not. And it is not clear whether the response is sufficient to start a 2-month or 6-month review.

BAXTER INTERNATIONAL – another company with problems in Puerto Rico

Baxter received a warning letter from the FDA about two of its plants in Puerto Rico, and the focus was on good manufacturing practice (GMP) violations, on distribution of materials to help customers with certain nutrition products, and on the failure to submit postmarketing reports. The products involved include the anesthetic Suprane (desflurane) and amino acid and critical care products. *Too many companies are having too many problems in Puerto Rico, raising a question of whether pharmas might look to move their plants somewhere else.*

Breast implants – linked to rare cancer

The FDA announced that it found an apparent association between breast implants (both saline and silicone) and anaplastic large cell lymphoma (ALCL), a very rare type of cancer. Worldwide, the FDA has identified ~60 cases of ALCL in the breasts of women with breast implants, a 2,000% increase from the expected rate in the general female population.

In a teleconference with reporters, Dr. William Maisel, chief scientist and deputy director for science in the FDA's Center for Devices and Radiological Health (CDRH), provided a few more details. What appeared most interesting was what he said about the possible mechanism of action for the ALCL – silicone in the cells of the tissue surrounding the implants but outside the implants.

- Most cases reviewed by the FDA were diagnosed when patients sought medical treatment for implant-related symptoms such as pain, lumps, swelling, or asymmetry that developed after their initial surgical sites were fully healed. These symptoms were due to peri-implant seromas, capsular contracture, or masses surrounding the breast implant. Examination of the fluid and capsule surrounding the breast implant led to the ALCL diagnosis.
- 34 of the 60 cases are from published literature. Of the 34, 24 were in silicone breast implant patients, 7 in saline implant patients, and 3 unspecified.
- The time from implant to ALCL varies from ~1 year to 23 years, with an average of ~8 years.
- There appears to be a link between silicone (perhaps the silicone coating, not the gel filling) and ALCL, but it is silicone nonetheless. Dr. Maisel said, "There is some suggestion that certain types of cells around the breast implants contain silicone, particularly [in cases of] implants that rupture, but even implants that don't rupture may have some of the silicone taken up by the cells. That chronic stimulation of the cells may have the possibility of inducing lymphoma in some cases…but we recognize that is speculative…We do know both silicone and saline implants are surrounded by silicone [coverings]…and contain other substances…Some of the silicone has been found in the cells around breast implants, and it is theorized this may be capable of stimulating cancer cells."
- While there appears to be a lower risk with reconstructive implants than cosmetic implants, Dr. Maisel declined to draw that conclusion. He said, "The number of cases is very small. It is hard to know precise numbers of women who got breast implants for a given reason…After our review, we don't believe there is a distinction to be made based on the reason for the implant."
- The ALCL association has developed since silicone implants were allowed back onto the market in 2006. Dr. Maisel said, "The vast majority [of ALCL cases] occurred after 2006." He specifically said that neither the information on the ALCL association nor any hint of it was available when the FDA made the decision to allow silicone implants back on the market and that this information developed after 2006.
- There is no link between breast implants and other lymphomas or any other cancers. In emphasizing this, Dr. Maisel said the association with ALCL has a "unique fingerprint" that is marked by "particular types of proteins on the outside of the cells" that suggests an association.

Asked whether there is an association between ALCL and ***textured*** *implants*, Dr. Maisel said, "Smooth vs. textured surfaces is another question that remains unanswered. In the literature, 4 [ALCL cases had implants that were] textured, but the remaining 30 did not say what type of surface they had. There are some reports in the scientific literature that textured surfaces may be more associated with ALCL, but after our review, we do not feel there is evidence of that being the case."

How bad is ALCL? The treatment options are chemotherapy, radiation, and surgery. Dr. Maisel said, "There is some suggestion from the literature that the scientific community believes that the form [of ALCL] associated with breast implants may be a less aggressive form of the disease, and there is some suggestion that removing the breast implants, the fluid, and the capsule may reduce the risk." But he quickly added, "The FDA does not feel comfortable recommending any specific treatment for all patients."

The FDA recommends that:

- Healthcare professionals report all confirmed cases of ALCL in women with breast implants to MedWatch.
- Healthcare professionals consider the possibility of ALCL if a patient has late-onset, persistent peri-seroma. If there is an implant seroma, the FDA recommends sending fresh seroma fluid for pathology tests to rule out ALCL.
- Women with breast implants do not need to change their routine medical care and follow-up.
- Women monitor their breast implants and contact their doctor if they notice any changes.
- Women considering breast implant surgery should discuss the risks and benefits with their healthcare provider.

What's next? "Later this year," the FDA plans to provide a "comprehensive update" of the *interim* findings of the post-marketing studies that are ongoing in the U.S. as well as an update on adverse events submitted to the FDA relating to breast implants. Dr. Maisel didn't give an exact date for this interim report, but he said a status report on the postmarketing studies would be given in spring 2011. However, he carefully avoided answering questions about the status of those post-marketing studies.

Meanwhile, the FDA will change the labels on **Mentor**'s and **Allergan**'s breast implants, and the Agency is working with the American Society of Plastic Surgeons to develop a registry of all breast implant patients.

The American Academy of Cosmetic Surgery (AACS) said it agrees with the FDA recommendations and hopes this report "does not produce undue panic from the millions of women who have breast implants." The AACS recently established a new task force on safety in cosmetic surgery and will continue to update its safety guidelines for cosmetic breast surgery as well as other cosmetic procedures. AACS also is implementing a new database reporting system for its members.

AACS also tried to put a more positive spin on things, commenting, "Awareness of breast cancer in general hopefully will increase women's desire for routine care and follow-up. This alone may be a good thing if it promotes early recognition and patient's awareness of any type of breast cancer regardless if women have implants or not."

Not surprisingly, Dr. Sidney Wolfe, director of Public Citizen's Health Research Group, thought the FDA action was too little, too late. He noted that Public Citizen petitioned the FDA in 1988 to ban silicone gel implants, warning of carcinogenicity – and sarcomas in particular – associated with the implants in animals: "Although today's FDA announcement is limited to lymphomas, not sarcomas, a possible link with implants of breast sarcomas in five women was published in 2009…Animal evidence of carcinogenicity, especially with the highly malignant tumors found in these studies, should be taken more seriously than the leadership in the FDA has done over the past two decades."

Deep Brain Stimulation – for treatment-resistant high blood pressure?

Researchers were surprised to discover what might be a potential new treatment for difficult-to-control high blood pressure, according to a case report published in ***Neurology***, the journal of the American Academy of Neurology. The report detailed the case of a 55-year-old man who received deep brain stimulation (DBS) for central pain syndrome that developed post-stroke. He had high blood pressure at the time of his stroke despite taking four antihypertensive medications.

DBS did not permanently alleviate the man's pain, but researchers were surprised to find that the brain stimulation gradually decreased his blood pressure, and eventually he was able to stop taking all of his antihypertensive medications. His blood pressure remained well controlled during the three years of follow-up. At one point he went back on one antihypertension drug briefly due to a slight increase in blood pressure, but the pressure came down and the drug was withdrawn.

The researchers tested turning off the stimulator, and that led to an average increase of 18 mmHg in systolic blood pressure and a 5 mmHg increase in diastolic blood pressure. When the stimulator was turned back on, his systolic blood pressure dropped by an average of 32 mmHg, and his diastolic blood pressured dropped 12 mmHg. Repeating the tests produced the same results.

Even if these results are confirmed, the therapy is a little bit drastic for any widespread use.

Drug-eluting stents – Maryland puts pressure on use

Dr. Joshua Sharfstein, secretary of Maryland's Department of Health and Mental Hygiene – and former FDA deputy commissioner – told the House Health and Government Operations Committee there are three ways to help with oversight of cardiac stent use:

- State health agencies could share confidential information about stent procedures in their state.
- Ban gifts from device companies to physicians.
- Create an accreditation process for cardiac cath labs in Maryland that perform stent procedures. While Dr. Sharfstein said this proposal might be premature, a state legislator is drafting a bill to set up an accreditation process for cath labs.

Electroconvulsive therapy (ECT) devices – FDA panel says don't ease approval pathway

The FDA's Neurological Devices Advisory Committee recommended that the FDA continue to regulate these devices as high-risk Class III devices. The exception might be devices for treating catatonia; the panel was divided on whether these devices should remain Class III or be reclassified as moderate-risk Class II devices.

Although ECT devices already are Class III, the FDA has been clearing them through the 510(k) pathway and not requiring a PMA. Two years ago, the Government Accountability Office (GAO) recommended that Class III devices require a PMA and not be allowed to use the 510(k) process. The FDA's advisory committee apparently agrees with the GAO.

GILEAD SCIENCES' Truvada (tenofovir + emtricitabine)

- **Application rejected.** The FDA rejected Gilead's application for a combination HIV pill combining Truvada and **Johnson & Johnson/Tibotec**'s TMC-278, a non-nucleoside reverse transcriptase inhibitor (NNRTI). The FDA asked for additional information about the chemistry and manufacturing of the proposed once-daily medication, and Gilead expects to submit that information by the end of March 2011.
- **New recommended guidelines.** The Centers for Disease Control and Prevention (CDC) is recommending that Truvada be given only for prevention to men who engage in high-risk sexual practices, including unprotected sex and multiple partners. This interim guidance was published in the CDC's ***Morbidity and Mortality Weekly Report*** on January 28, 2011. Formal U.S. Public Health Service guidelines are expected to be issued later this year.

NIH – creates new drug discovery center

The National Institutes of Health is getting a new center, the National Center for Advancing Translational Sciences. Concerned about the slowing pace of new drugs coming from pharma, the government is creating this center to help create new medications, funding it with an initial $1 billion. The new center will do as much research as needed to attract pharma investment in an experimental drug.

SANOFI-AVENTIS

- **Allegra (fexofenadine)** is going over-the-counter.
- **Iniparib (BSI-201)**, a PARP inhibitor, missed both co-primary endpoints in a 519-patient Phase III trial in late-stage breast cancer, failing to significantly improve survival or slow disease progression.
- **Multaq (dronedarone) –** The European Committee for Medicinal Products for Human Use has begun reviewing the risk:benefit profile of this cardiac medication after reports of acute liver damage in two patients. The committee is calling for "urgent regulatory action."
- **Plavix (clopidogrel) –** No generic versions will be available in the U.S. before May 16, 2012, six months longer than expected, because the FDA granted the company an additional six months of pediatric exclusivity.

VIVUS's Qnexa (phentermine + topiramate) – more safety analysis needed

The FDA is still seeking more safety information on this diet drug. Vivus says the FDA now wants to use its existing databases to determine the risk of oral cleft palate in children whose mothers took topiramate to prevent migraines. That analysis could take six months. Vivus says no birth defects were seen in the 15 live births seen in its clinical trials. Vivus didn't say anything about the FDA's earlier concerns about cardiovascular risk.

REGULATORY NEWS

CMS: President still backing Berwick

President Obama renominated Dr. Donald Berwick to head the Centers for Medicare and Medicaid Services (CMS). Senate Republicans strongly objected to Berwick's appointment last year, pointing to his previous comments in support of the British health system and rationing.

CMS still studying imaging utilization

CMS is holding a "listening session" on January 31, 2011, to discuss whether to add several new imaging studies to its data reporting program that tracks overutilization, the Hospital Outpatient Quality Data Reporting program. At the session, CMS is asking for input on:

- Which other imaging procedures would be appropriate candidates for efficiency measures.
- Whether there are certain diseases that should be examined from the perspective of imaging use for diagnosis.
- Whether CMS should examine imaging efficiency not just in hospitals but in other settings, such as independent diagnostic testing facilities or physician offices.

FDA: all chronic fatigue drugs to be handled by one division

The FDA announced that, effective immediately, all new drugs and biologics to treat chronic fatigue syndrome (CFS) will be reviewed by the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP), regardless of the proposed action or the primary endpoint in the clinical trial. Existing active applications (both NDAs and INDs) are being transferred to DPARP.

Until now, CFS drugs have been handled by at least six different FDA divisions within the Office of New Drugs, and they have utilized a variety of primary endpoints. The FDA, however, is open to development of a validated measure of patient reported outcomes.

FDA's Mini-Sentinel guinea pig is Onglyza

AstraZeneca/Bristol-Myers Squibb's Onglyza (saxagliptin), a diabetes drug, was chosen as the test drug for the first phase of the FDA's Sentinel real-time drug surveillance program. Mini-Sentinel is the pilot program to access patient databases maintained by health plans and other organizations and to track events and query claims anonymously. Onglyza reportedly was chosen because the 12,000-patient, 5-year, Phase IV, SAVOR safety trial of Onglyza was ongoing and because the drug's premarket safety looked pretty clean.

PhrMA lobbying to kill Medicare IPAB

The Pharmaceutical Research and Manufacturers of America (PhrMA), along with the American Medical Association (AMA) and the American Hospital Association (AHA) and others, is lobbying Congress to weaken or cancel the Medicare Independent Payment Advisory Board (IPAB), which was created to control costs. The House is expected to attempt to repeal the relevant provision this year, and some Democrats might support the repeal.

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
	January 2011	
January 31	**Orexigen Therapeutics' Contrave** (naltrexone + bupropion), a diet drug	PDUFA date
	February 2011	
February 8	Review of **postmarketing studies for cancer drugs** receiving accelerated approval prior to January 1, 2009	FDA's Oncologic Drugs Advisory Committee (ODAC)
February 9	Public workshop on expanding ***in vivo* biomarker detection devices**, focusing on research opportunities and technical challenges	FDA and the Defense Advanced Research Projects Agency (DARPA)
February 12	Presentation of full details of Phase III trial of **Regeneron Pharmaceuticals/Bayer's afilbercept** (VEGF Trap-Eye)	Angiogenesis, Exudation, and Degeneration 2011 conference at Bascom Palmer Eye Institute in Miami
	March 2011	
March 2	Discussion of **innovative approaches to the development of drugs for orphan and rare disease**, including how to utilize biomarkers and pharmacogenetics	FDA Pharmaceutical Sciences and Clinical Pharmacology Advisory Committee meeting in Dallas, Texas
March 5 (approx.)	**Merck KGaA's cladribine** for multiple sclerosis	PDUFA date
March 7	**Salix Pharmaceuticals' Xifaxan** (rifaximin) for non-constipation IBS	PDUFA date
March 8	**Novartis's Arcapta Neohaler** (indacaterol maleate), a QD bronchodilator for long-term use in COPD	FDA's Pulmonary-Allergy Drugs Advisory Committee
March 10	Risk of **neurodegeneration in pediatric patients** from anesthetic drugs	FDA's Anesthetic and Life Support Drugs Advisory Committee
March 10	**GlaxoSmithKline's Lamictal XR** (lamotrigine extended-release) and discussion of use of historical-controlled trials as a comparator for anticonvulsant monotherapy in epileptic seizures	FDA's Peripheral and Central Nervous System Drugs Advisory Committee
March 10	**Human Genome Sciences/GSK's Benlysta** (belimumab) for lupus	PDUFA date
March 16	Preliminary decision on **how to cover ESAs** for kidney disease patients	CMS decision
March 26	**Bristol-Myers Squibb's Yervoy** (ipilimumab) for advanced melanoma	PDUFA date
	April 2011	
April 5	**Optimer Pharmaceuticals' fidaxomicin** for the treatment of *C. diff*	FDA Anti-Infective Drugs Advisory Committee
April 7	**AstraZeneca's Zactima** (vandetanib) for inoperable medullary thyroid cancer	PDUFA date
April 7-8	**FDA 510(k) reform**	FDA public meeting
April 10	Open forum to discuss statistical issues related to **drug and biologics development and review**	Joint FDA and Drug Information Agency Forum
April 13	**KV Pharmaceutical/Hologic's Gestiva** (17-alpha hydroxyprogesterone) to prevent premature birth	PDUFA date
	Other future 2011 meetings/events	
May 23	**Vertex Pharmaceuticals' telaprevir**, a treatment for hepatitis C	PDUFA date
May 30	**Optimer Pharmaceuticals' fidaxomicin** for the treatment of *C. diff*	PDUFA date
June 16	Final decision on **coverage of ESAs** for kidney disease patients	CMS decision
June 23	**Pfizer/King Pharmaceuticals/Pain Therapeutics' Remoxy** (tamper-resistant oxycodone CR) for pain	PDUFA date
Summer	Report on **FDA 510(k) reform**	Institute of Medicine
2H11	**Abbott's RX Acculink** carotid stent	FDA final decision expected
October 20	**Johnson & Johnson's abiraterone** for metastatic prostate cancer	PDUFA date