TRENDS-in-MEDICINE

March 27, 2011

by Lynne Peterson

Quick Takes

…Highlights from this week's news affecting drugs and devices in development that are not covered in longer *Trends-in-Medicine* reports…

SHORT TAKES

- **Alzheimer's disease –** According to a study of mice published in ***Nature Biotechnology***, exosomes may be a way to deliver drugs to the brain. Oxford researchers reportedly were able to switch off a gene implicated in Alzheimer's in the brains of mice by injecting exosomes that carried a drug across the normally impermeable blood brain barrier. *Of course, this hasn't been tested yet in humans, but the idea is intriguing.*

- **Biofilm on medical devices –** According to a report in the journal ***Antimicrobial Agents and Chemotherapy***, the active ingredient from a plant commonly used in Chinese medicine – 1,2,3,4,6-Penta-O-galloyl-beta-D-glucopyranose (PGG) – prevents biofilm formation by *Staphylococcus aureus* on polystyrene and polycarbonate surfaces as well as silicon rubber (which is used in catheters). PGG doesn't kill *S. aureus*, just prevents its attachment to devices. *This could really be useful for numerous devices.*

- **BRISTOL-MYERS SQUIBB's Yervoy (ipilimumab) –** The FDA approved this BRAF inhibitor for the treatment of advanced melanoma. The company announced earlier this week that a new study found that adding Yervoy to standard chemotherapy for metastatic melanoma improved survival vs. standard chemotherapy alone. The full data are expected to be presented at the American Society of Clinical Oncology meeting in June.

- **GILEAD SCIENCES' elvitegravir** given once daily showed non-inferiority to **Merck**'s Isentress (raltegravir), which is given twice daily, in a 48-week Phase III study of 702 treatment-experienced HIV patients.

- **GLAXOSMITHKLINE's Avodart (dutasteride) –** The company is giving up plans worldwide to seek an expanded indication for this benign prostatic hyperplasia (BPH) drug to treat prostate cancer. In January an FDA advisory committee voted against the expanded indication, and more recently Swedish regulators informally rejected the idea.

- **GW PHARMACEUTICALS' Sativex (an oral cannabinoid-based spray)** was recommended for approval in six European countries – including Germany, Denmark, and Sweden, where it is expected to start being sold in 2011, and in Austria, the Czech Republic, and Italy, where sales are expected to start in 2012 – to treat spasticity in multiple sclerosis patients. **Bayer** has the marketing rights for this under-the-tongue spray in the U.K., and **Almirall** has the rights in other European countries.

- **HIV drugs –** A Texas Senate Medicaid subcommittee voted to increase state spending on healthcare programs such as for mental health and foster parents, etc., by $4.5 billion, but the subcommittee cut a program that supplies HIV drugs to 14,000 poor people.

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- **ICAD/XOFT's Axxent FlexiShield Mini** – This device to shield healthy breast tissue from radiation treatment of breast cancer was pulled from the U.S. market in February 2011 after 30 patients in a trial were found to have tungsten particles in their breasts. The FDA said its toxicologists have not found evidence that the heavy metal harmed the study participants.

- **LUCIGEN** received a $226,401 grant from the National Institutes of Health to develop improved genomic tools to study possible antibiotic compounds in fungi.

- **MERCK and TEVA's NOMAC-E2,** a birth control pill with estrogen that is reported to be structurally identical to the major estrogen produced by the ovaries of healthy non-pregnant women, got a positive recommendation from the Committee for Medicinal Products for Human Use of the European Medicines Agency (EMA). The pill is in Phase III testing in the U.S.

- **OXIGENE's Zybrestat (vascular disrupting agent)** – Last month the company cut its staff by 50% and said it would stop enrollment in a Phase II trial of this thyroid cancer treatment, but after meeting with the FDA this week, the company said the FDA believes there is hope for the drug, though a new trial would be needed for approval. And the Agency said the design of the Phase II trial would not be sufficient, so the new trial will have to have a different design. It is not clear yet whether Oxigene can find the funding to do that.

- **PORTOLA PHARMACEUTICALS' betrixaban** – **Merck** decided it doesn't want to collaborate any longer on this anticoagulant for atrial fibrillation patients. Merck reportedly returned the rights to the drug as part of its ongoing "prioritization" process.

- **PROCTER & GAMBLE (P&G)** and **Teva** plan to collaborate on over-the-counter (OTC) products, including Vicks and Pepto-Bismol. The two companies are combining their OTC drug businesses outside of North America, with a particular focus on Germany, Russia, and Brazil.

- **REGEN BIOLOGICS' Menaflex** – The company declined an FDA offer of a hearing on this meniscus implant, saying the hearing wouldn't be helpful, and opted out of the administrative process in lieu of other, unspecified legal options. The FDA is considering nullifying the 510(k) clearance for Menaflex.

- **SAVIENT PHARMACEUTICALS' Krystexxa (pegloticase)** – The company said it secured a contract with the U.S. Department of Veterans Affairs to supply this gout drug – as well as its weight-gain drug Oxandrin (oxandrolone) – for five years.

- **TAKEDA's Actos (pioglitazone)** – The EMA is looking into the risk:benefit profile of this Type 2 diabetes drug after a spike in reports possibly linking it to an increased risk of bladder cancer.

- **TARGACEPT's TC-5619** missed the primary endpoint in a 135-patient, proof-of-concept Phase II trial in attention deficit/hyperactivity disorder (ADHD).

- **TOMOTHERAPY's Hi-ART System** – A recall is under way of 326 units because the FDA determined that the Treatment Planning Station for this radiation delivery system can potentially under dose radiation.

- **Vaccines** – Japanese regulators are allowing the resumption of sales of **Pfizer's Prevnar** (pneumococcal 7-valent conjugate) and **Sanofi's ActHIB** (haemophilus b conjugate vaccine), which is distributed in Japan by Daiichi Sankyo.

- **WALGREENS** is buying **Drugstore.com**, an online pharmacy.

- **XENOPORT's arbaclofen placarbil** – The company is abandoning development of this treatment for severe gastroesophageal reflux disease (GERD) after a Phase II trial failed to show superiority to placebo at any of four doses tested.

- **XOMA's Xoma-052** missed the primary endpoint in a 6-month, 410-patient trial in Type 2 diabetes, failing to lower HbA_{1c} more than placebo. However, the drug lowered CRP and increased HDL, so it may still have utility in coronary disease or eye inflammation.

NEWS IN BRIEF

ABBOTT's TriCor (fenofibrate) and Trilipix (fenofibric acid) – use tripled *without* efficacy data

Data from an IMS database indicate that monthly prescriptions for these two drugs increased in the U.S. from 150 to 550 per 100,000 people from 2002 to 2009 even though two major studies – FIELD in 2004 and ACCORD in 2010 – found the drugs did not reduce cardiovascular events. In an article in the ***Journal of the American Medical Association***, Cynthia Jackevicius, PharmD, of Western University of Health Sciences in Pomona CA and colleagues said the data should have discouraged prescribing. In contrast, in Canada prescriptions remained fairly constant at 200 per 100,000 people.

ACE + ARB = kidney problems

An analysis of nearly 32,000 patients over 55 months from a Canadian database found that hyperkalemia and renal

dysfunction occurred twice as often in older patients treated with both an ACE inhibitor and an angiotensin receptor blocker (ARB) than with either drug alone (HR 2.36). The study was published in the ***Canadian Medical Association Journal***.

ALLERGAN's Lap-Band – lack of long-term efficacy?

A study of **BioEnteric**'s lap-band (now owned by Allergan) in 82 patients found that 50% of these obesity devices had to be removed due to erosion or malfunction, 39% of patients had a major complication, and 60% of patients had at least one reoperation for complications or device failure. The study was published in the ***Archives of Surgery***. The Belgian researchers concluded, "The high failure rate of laparoscopic adjustable gastric banding, at least in our hands, could be detrimental to its future continued widespread use as a restrictive weight-loss operation…The use of wider, softer bands provide better overall results than the 'perigastric' technique that we used at the time."

On the positive side, 60% of patients were pleased or very pleased with their original lap-band procedure, patients lost an average of 42.8% of their original excess weight, and mean body mass index (BMI) was reduced by 7.8 points.

CEPHALON – two pieces of positive news

- Cephalon is acquiring **Gemin X Pharmaceuticals**, an oncology company whose lead compound is probably obatoclax, a treatment for small cell lung cancer.
- A federal judge in Delaware ruled that **Watson Pharmaceuticals**' proposed version of Cephalon's cancer-pain drug Fentora (fentanyl buccal) infringes on a Cephalon patent that doesn't expire until 2019 and which covers the process that makes the tablet dissolve.

Diet drugs – looking for a pathway forward

Officials of four associations concerned with obesity – the Obesity Society, the Obesity Action Coalition, the American Society for Metabolic and Bariatric Surgery, and the American Dietetic Association – met with Janet Woodcock, MD, director of the FDA's Center for Drug Evaluation and Research (CDER), to try to find a way forward for new obesity drugs after three drugs that had looked promising were all rejected by the Agency. No specific actions came out of the meeting, but the officials seemed pleased with the meeting. One *suggestion* they made was to allow approval of drugs based on improvements in specific comorbidities, such as sleep apnea, but Dr. Woodcock didn't commit to that pathway.

GENZYME – mixed news

- **Fabrazyme (agalsidase beta)** – The Massachusetts plant that produces this Fabry's disease treatment had a production setback – the rejection of a single lot due to a quality issue.
- **Plerixafor (AMD-3100)**, a CRCX4 inhibitor originally investigated as a treatment for HIV, may make morphine safer and more effective. Researchers at the Indiana University School of Medicine, funded by the National Institute on Drug Abuse, published data in ***Brain, Behavior, and Immunity*** which found that, at least in rats, AMD-3100 reduced opioid-induced hyperalgesia, suggesting it could be used to reduce this problematic side effect of morphine.

JOHNSON & JOHNSON/ETHICON

- **Sedasys – a new FDA review.** The company appealed the FDA's rejection of this computer-assisted personalized sedation system, and the Agency has scheduled an advisory committee to review it again. Sedasys was designed for gastroenterologists to use to deliver propofol for minimal-to-moderate sedation in healthy patients undergoing a colonoscopy or esophago-gastroduodenoscopy. It had been submitted as a PMA, and in February 2010 the Center for Devices and Radiologic Health (CDRH) issued a not-approvable letter, saying there wasn't sufficient proof of safety.

  The findings of the advisory committee will be submitted to FDA Commissioner Margaret Hamburg, MD, and both the company and CDRH will then have an opportunity to comment (in writing) on the committee's finding. Then, Dr. Hamburg will make the final decision on the device. No date for the advisory committee meeting has been set yet.
- **The J&J weekly recall:** Medical drainage products from Ethicon are being recalled due to sterility concerns.

L-methylfolate – *possible* benefit in MDD

Data from two multicenter Phase II trials presented at the European Congress of Psychiatry suggest this folate ***may*** help major depressive disorder (MDD) patients who were partial responders or non-responders to SSRIs, but only at the higher dose tested. The studies' co-primary endpoints were (a) response rate and (b) an improvement of ≥50% (or a final score of ≤7) on the Hamilton Depression Rating Scale (HDRS-17).

- TRD-1 trial – a 148-patient, 60-day study of a 7.5 mg/day dose in Phase I and a 15 mg/day dose in Phase II. This missed the primary endpoint.

- TRD-2 trial – a 60-day study of 15 mg/day in 75 patients. This trial met the primary endpoint (p=0.04 and p=0.05, respectively, on the co-primary endpoints).

MATRIXX INITIATIVES – shareholder lawsuit to proceed

The U.S. Supreme Court decided that shareholders ***can*** sue **Matrixx** for not disclosing adverse events (specifically, not telling them that several patients lost their sense of smell) after taking Zicam, a zinc-based cold remedy. The company argued that disclosure is required only when side effects are statistically significant, but Justice Sonia Sotomayor wrote, "Given that medical professionals and regulators act on the basis of evidence of causation that is not statistically significant, it stands to reason that in certain cases reasonable investors would as well…[But this] does not mean that pharmaceutical manufacturers must disclose all reports of adverse events." *The question is whether this will lead to more adverse event transparency at other companies.*

NOVARTIS

- **Gilenya (fingolimod)** was cleared by European regulators for use in multiple sclerosis patients with active or severe forms of relapsing-remitting multiple sclerosis – second line in patients who have tried beta interferon or first line when the disease is rapidly evolving. This is a narrower approval than in the U.S.
- **Arcapta Neohaler (indacaterol) –** The FDA delayed the PDUFA date from April to July 2011 for this once-daily long-acting beta agonist (LABA). Earlier this month, the FDA's Pulmonary-Allergy Drugs Advisory Committee recommended approval of the low dose (75 µg QD) but not the high dose (150 µg) that is approved in Europe. The concern with the higher dose was lack of sufficient long-term follow-up showing it is safe or more effective than the lower dose.

PFIZER

- **CP-870,893**, in combination with **Lilly**'s Gemzar (gemcitabine), shrank pancreatic tumors in a study published in the journal ***Science***. In addition, time to disease progression was longer with the chemo than Gemzar alone (5.6 months vs. 2.3 months). However, all the patients eventually relapsed (progressed).
- **Fragmin (dalteparin) –** A 3,764-patient multicenter study published in the ***New England Journal of Medicine*** found that this subcutaneous QD low molecular weight heparin was ***not*** superior to BID unfractionated heparin (UFH) for preventing deep vein thrombosis (DVT) in critically ill patients. Proximal DVT developed in 5.1% of dalteparin patients vs. 5.8% of UFH patients (HR 0.92, p=0.57). However, there were significantly fewer pulmonary embolisms with dalteparin (1.3% vs. 2.3%, p=0.01).

Proton pump inhibitors (PPIs) – low fracture risk with OTC PPIs

The FDA reversed itself, saying now that short-term use of low-dose, over-the-counter PPIs – which are marketed for 14-day courses up to three times a year – is "unlikely" to lead to hip, wrist, and spine fractures. Last year the FDA added a fracture warning to ***all*** PPIs. Now, the FDA believes that the patients at highest risk for fractures are those who take high doses or use a prescription PPI for at least a year.

ROCHE

- **PLX-4032 –** In a study published in the journal ***Nature***, researchers reported that leflunamide, a generic arthritis drug, inhibited the growth of melanomas in mice. And the researchers also combined leflunamide with PLX-4032, a BRAF inhibitor produced in partnership with Plexxikon and Daiichi Sankyo, suggesting the combination may be even more effective than either alone.
- **Vismodegib (RG-3616/GDC-0449) –** The pivotal Phase II ERIVANCE trial of this hedgehog pathway inhibitor met the primary endpoint (overall response rate), shrinking tumors in advanced/metastatic basal cell carcinoma patients. No new side effects emerged. ERIVANCE was an international, single-arm, multicenter, two-cohort, open-label study of 104 patients. Vismodegib was dosed 150 mg QD until disease progression.

SHIRE's Firazyr (icatibant) – new hope for this drug?

A 98-patient, international, double-blind trial (FAST-3) found that a single injection of Firazyr (3 ml) resolved hereditary angioedema attacks faster than placebo (2.0 hours vs. 19.8 hours, p<0.001). This comes after two previous pivotal studies (FAST-1 and FAST-2) showed conflicting efficacy results, resulting in an FDA rejection in 2008.

Researchers from the University of Texas Southwestern Medical Center in Dallas reported at the American Academy of Allergy, Asthma, and Immunology meeting that composite visual analog symptom scores dropped during the first four hours and remained significantly lower than placebo at every time point out to 12 hours. Firazyr also was significantly better than placebo on several secondary endpoints:

- Time to initial symptom relief (0.8 vs. 3.5 hours, p<0.001).

- Time to onset of primary symptom relief (1.5 vs. 18.5 hours, p<0.001).
- Time to "almost complete" symptom relief (8.0 vs. 36.0 hours, p=0.012).

TERUMO CARDIOVASCULAR SYSTEMS – gets FDA injunction and consent decree

The FDA announced that the company, which makes heart-lung bypass machines, and two of its officers (president/CEO Mark Sutter and vice president Mark Lincoln) signed a consent decree of permanent injunction prohibiting the manufacturing or distribution of two heart-lung bypass systems and other cardiovascular devices to new customers. The consent decree also restricts the sale of these systems to existing customers until Terumo complies with the FDA's current Good Manufacturing Practice (cGMP) and Medical Device Reporting (MDR) requirements.

Terumo also was fined $35 million. The devices are not being removed from the market because of the FDA's concern of possible device shortages if that were done. Terumo received warning letters in 2004 and 2006, but inspections in early 2010 found "numerous" cGMP and MDR violations at the company's plant in Michigan. *Why don't companies take these letters seriously?*

REGULATORY NEWS

Clinical trials registry for Europe: www.clinicaltrialsregister.eu

In response to calls for more openness and transparency, the EMA has launched an online, searchable clinical trials registry, EU Clinical Trials Register, similar to www.clinicaltrials.gov in the U.S. The site will contain information about clinical trials conducted by industry or researchers that are authorized in the European Union, whether they take place in one member state or in several. The entries are not necessarily in English.

FDA restricts Japanese food imports to U.S.

The FDA, concerned about possible radiation contamination, will detain all dairy products, fruits, and vegetables that originated near the Fukushima nuclear reactors in Japan. The items will be quarantined at U.S. ports to prevent their distribution in the U.S. Among the food items in which elevated radiation levels have been detected so far are milk, broccoli, beans, spinach, fish, and local drinking water.

FDA warning letters

The FDA regularly sends warning letters to companies whose drugs or devices are not in compliance with FDA regulations. Among the companies/products receiving letters recently were **Nanotherapeutics**' Origen and NanoFuse demineralized bone matrix products – because the company did not submit a PMA, modified Origen without notifying the FDA or submitting a new 510(k) application, misbranded the products, and did not keep adequate records.

Harmonization effort excludes device manufacturers

The Global Harmonization Task Force (GHTF), a regulatory group that reconciles device regulations in various countries, notified its device industry partners, including the Medical Imaging and Technology Alliance, that they will no longer be invited to participate in the steering committee or task force activities. The GHTF also plans to reorganize to include regulatory officials from more countries.

Bill would require Medicare to cover off-label drugs

Legislation proposed by Rep. Mac Thornberry (R-TX) and Rep. Russ Carnahan (D-MO) would expand Medicare drug coverage to include off-label use provided efficacy is documented in sources such as peer-reviewed medical journals. Earlier this month, a federal judge ruled that Medicare is required to cover drugs used off-label if the drugs are considered medically necessary.

U.K.'s NICE to expand Alzheimer's drug coverage

The U.K.'s National Institute of Health and Clinical Excellence (NICE) decided that **Pfizer**'s Aricept (donepezil), **Johnson & Johnson**'s Razadyne (galantamine, formerly Reminyl), and **Novartis**'s Exelon (rivastigmine) should be reimbursed for patients with mild Alzheimer's disease as well as moderate-to-severe disease. And NICE is also expanding coverage for **Forest Laboratories/Lundbeck**'s Namenda/Ebixa (memantine) to patients with moderate symptoms, not just late-stage disease.

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
April 2011		
April 2	**Novartis's Gleevec** (imatinib) for GIST	PDUFA date
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	Online repository of **searchable 510(k) medical device labels and photographs**	FDA's Center for Devices and Radiological Health (CDRH) public meeting
April 10	Open forum to discuss statistical issues related to **drug and biologics development and review**	Joint FDA and Drug Information Agency (DIA) Forum
April 12	**NDA for Novartis's Afinitor** (everolimus) and **sNDA for Pfizer's Sutent** (sunitinib) to treat neuroendocrine tumors	FDA's Oncologic Drugs Advisory Committee
April 13	**KV Pharmaceutical/Hologic's Gestiva** (17-alpha hydroxyprogesterone) to prevent premature birth	PDUFA date
April 14-15	**Cardiovascular Safety and Drug Development:** QT, arrhythmias, thrombosis, and bleeding	Joint FDA/DIA meeting
April 27	**Merck's Victrelis** (boceprevir) for HCV	FDA's Antiviral Advisory Committee
April 27	**Medicis Aesthetics' Restylane** – expanded indication for augmentation of the lips	FDA's General and Plastic Surgery Devices Advisory Committee
April 28	**Vertex Pharmaceuticals' telaprevir** for HCV	FDA's Antiviral Advisory Committee
Other future 2011 meetings/events		
May 4-5	**Biosimilar challenges and opportunities**	Joint DIA and FDLI conference
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 17	**Celgene's Istodax** (romidepsin) – sDNA for peripheral T-cell lymphoma	PDUFA date
June 17	**Pfizer/King Pharmaceuticals' Acurox** (immediate-release oxycodone), a painkiller	PDUFA date
June 23	**Pfizer/King Pharmaceuticals/Pain Therapeutics' Remoxy** (tamper-resistant oxycodone CR) for pain	PDUFA date
June 28-29	**Roche/Genentech's Avastin** (bevacizumab), hearing on appeal of FDA's decision to withdraw the indication for metastatic breast cancer	FDA's Oncologic Drugs Advisory Committee (ODAC)
July	**Novartis's Arcapta Neohaler** (indacaterol) long-acting beta agonist (LABA) for COPD	PDUFA date
July 20	**AstraZeneca's Brilinta** (ticagrelor), an anticoagulant	PDUFA date
August 25	**Shire's Firazyr** (icatibant) for hereditary angioedema	PDUFA date
2H11	**Abbott's RX Acculink** carotid stent	FDA final decision expected
Summer	Report on **FDA 510(k) reform**	Institute of Medicine
4Q11	**Ophthotech's ARC-1905** primary endpoint results in Phase I trial in dry AMD	Company announcement or medical conference presentation
4Q11	**Roche/Genentech's Lucentis** (ranibizumab) – Phase III HARBOR trial one-year data on the 2 mg dose in wet AMD	Company announcement or medical conference presentation
October 20	**Johnson & Johnson's abiraterone** for metastatic prostate cancer	PDUFA date
December	**Allergan's brimonidine tartrate intravitreal implant** – Phase II trial in dry AMD to complete	Company announcement or medical conference presentation
2012 meetings/events		
February 2012	**Alcon's tandospirone** for dry AMD – Phase III final data expected	Company announcement or medical conference presentation