TRENDS-in-MEDICINE

May 15, 2011

by Lynne Peterson

Quick Takes

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

SHORT TAKES

- **3M's BacLite** – The U.K. government and the Porton Group urged the FDA to investigate how 3M performed a clinical trial of this device to detect methicillin-resistant Staphylococcus aureus, claiming the company "botched" the study. However, 3M says the device simply failed to meet expectations.
- **ABBOTT VASCULAR** is voluntarily recalling 500 of its MitraClip mitral valve repair systems due to problems with the delivery catheter.
- **ALKERMES and ELAN DRUG TECHNOLOGIES** are merging. The combined company will be incorporated in Ireland and called **Alkermes Plc**. Elan will own a 25% stake. The deal is expected to close in 3Q11. Elan will then focus entirely on its biotechnology business.
- **ALLERGAN's Latisse (topical bimatoprost)** – Allergan plans to start a clinical trial next month of this eyelash lengthener as a treatment for baldness and hopes to get FDA approval by 2013.
- **AMYLIN PHARMACEUTICALS' Symlin (pramlintide acetate)** – Amylin is planning a trial in which Type 1 diabetics will get both insulin and Symlin to see if the combination injection works the same or better at controlling glucose levels as separately injected doses of the therapies.
- **Anesthesia drug shortage** – A poll of 1,373 anesthesiologists (1,350 in the U.S.) by the American Society of Anesthesiologists found that >90% are experiencing a shortage of at least one anesthetic, particularly neostigmine (57%), thiopental (55%), succinylcholine (48%), propofol (40%), and glycopyrrolate (17%).
- **BAYER's regorafenib**, which already has orphan drug status, was granted fast track status for advanced and/or unresectable gastrointestinal stromal tumors (GIST). A Phase III trial in combination with best supportive therapy is under way.
- **BIOMIMETIC's Augment** – The FDA's Orthopaedic and Rehabilitation Devices Advisory Committee was split 10-8 on the effectiveness of this bone graft device for foot and ankle surgery. While some panel members decided it is a safe and effective alternative to autograft, others were critical of the study and the efficacy.
- **BOSTON SCIENTIFIC** announced that Ray Elliott will retire as president and CEO on December 31, 2011. The company's board has created a special CEO search committee, on which Elliott will serve as a member, to select its next president and CEO.

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- **DAVITA** – The federal government is investigating whether this kidney dialysis company overprescribed **Amgen**'s Epogen (epoetin alfa), but the company denies any wrong-doing, saying its use of EPO has followed medical research and practice.

- **ENDO PHARMACEUTICALS' Opana ER (oxymorphone extended-release)** has replaced **Purdue Pharma**'s OxyContin (oxycodone) as the drug of choice by drug abusers in Nassau County (Long Island) NY. From August 2010 to February 2011, local officials say, Medicaid prescriptions of OxyContin declined 43% while Medicaid prescriptions for Opana, which is twice as strong and a fraction of the cost of OxyContin, increased 45%.

- **FOREST LABORATORIES** – The Assistant U.S. Attorney for the District of Massachusetts issued a subpoena to Forest, seeking documents related to the company's off-label marketing of high blood pressure drugs Benicar (olmesartan medoxomil), Benicar HCT (olmesartan medoxomil-hydrochlorothiazide), and Azor (amlodipine + olmesartan).

- **JOHNSON & JOHNSON's weekly recall: Prezista (darunavir)** – The company recalled >11,000 bottles of this HIV/AIDS drug after consumer reports of musty or moldy odors, again probably caused by a chemical on the shipping pallets.

- **MEDTRONIC's new CEO**, effective June 13, 2011, will be Omar Ishrak, former president and CEO of **GE Healthcare Systems**.

- **MITHRIDION's MCD-386CR**, for progressive supranuclear palsy, a rare brain disease, was granted orphan drug status.

- **Peripheral stenting** – A study presented at the Society for Cardiovascular Angiography and Interventions (SCAI) meeting found stenting is safe and is more effective than balloon venoplasty alone for patients with a deep vein thrombosis (DVT) in the femoropopliteal vein, though it is not the first option. The randomized, 141-patient, 3-year EVISTA-DVT trial found the recurrence of DVT was 4% for stenting vs. 10% with balloon treatment.

- ***Pf*ēNEX** announced a three-year strategic collaboration with **AstraZeneca/MedImmune** that gives MedImmune non-exclusive access to *Pf*ēnex Expression Technology and scientific resources for the development of bioprocesses for human therapeutic proteins and vaccines. *Pf*ēnex will engineer production strains and develop early production processes for MedImmune's proprietary molecules. A Joint Steering Committee will be established to oversee the collaboration and facilitate the decision-making process.

- **RIGEL PHARMACEUTICALS' R343** – **Pfizer** has returned the rights to this allergic asthma treatment to Rigel, which is expected to start a Phase II trial later this year.

- **SANOFI-AVENTIS changed its name**; it is now just **Sanofi**.

- **SERVIER's Mediator (benfluorex)** – The French government accused Servier of hiding the potential risks of this diabetes drug, which has been linked to as many as 2,000 deaths, by wrongly promoting it. French officials said Mediator is a "potent" appetite suppressant similar to fen-phen, which was withdrawn in the U.S. in 1997 due to valvulopathy. Servier denied the allegation and said it has acted responsibly.

- **TAKEDA PHARMACEUTICAL** is in talks to buy privately held Swiss rival **Nycomed**.

- **VIROPHARMA's Cinryze (C1 esterase inhibitor)** – Currently, this treatment for hereditary angioedema is administered by IV, but ViroPharma wants to develop a formulation patients can inject themselves. To that end, ViroPharma licensed a compound from **Halozyme** that may help deliver the drug in an injectable formulation.

- **WRIGHT MEDICAL** – The U.S. Attorney's Office for the District of New Jersey claims Wright Medical breached a deferred prosecution agreement reached in 2010 to resolve allegations that it gave doctors kickbacks to ramp up the sales of its joint implants.

NEWS IN BRIEF

Acetaminophen – linked to hematologic cancers

Regular, long-term use may increase the risk of hematologic cancers, University of Washington researchers reported in the ***Journal of Clinical Oncology***. While the researchers found an association between acetaminophen and hematologic cancers, they didn't prove a cause-and-effect relationship.

The researchers reviewed data on 64,839 men and women age 50-76 from the Vitamins and Lifestyle (VITAL) study, identifying 577 cases of cancers. They found an almost two-fold increased risk for some hematologic cancers, such as myeloid neoplasms, non-Hodgkin's lymphoma, and plasma cell disorders – but not chronic lymphocytic leukemia (CLL) – in people who used acetaminophen ≥4 days/week over four years.

They did not find the same increased risk with the heavy use of aspirin, other NSAIDs, or ibuprofen.

California – could end copays for some drugs

A bill making its way through the California legislature would ban copays for drugs that fall into "specialty tiers," which would include many drugs for cancer, multiple sclerosis, scleroderma, rheumatoid arthritis, etc. Instead, the legislation would impose a $150/month out-of-pocket cap on medications for all patients.

CHEMGENEX's Omapro (omacetaxine mepesuccinate for injection) – FDA issues warning letter

The FDA sent the company a warning letter that a brochure at the American Society for Hematology meeting in December 2010 contained claims for this unapproved treatment for chronic myelogenous leukemia (CML) and other hematologics that were false and misleading. The FDA issued a complete response letter for Omapro in April 2010, citing concerns with an incomplete efficacy study, safety, insufficient *in vitro* testing, etc.

HIV vaccine – effective in monkeys

An article in the journal ***Nature*** reported on research showing a vaccine containing a genetically modified form of rhesus CMV (cytomegalovirus) protected macaques against the monkey equivalent of HIV, suggesting a fresh approach to a human HIV vaccine. In 13 of the 24 monkeys, the vaccine knocked out the virus, and it provided protection for at least a year in 12 of those. CMV works by priming the immune system to quickly attack the HIV virus when it first enters the body, when it is most vulnerable.

MELA SCIENCES' MelaFind – asking for senior FDA intervention

The company asked FDA Commissioner Margaret Hamburg, MD, to be involved in the review of its premarket approval application for this melanoma detection device. In November 2010, an FDA advisory committee was split (8-7) on the approvability of this device, after FDA reviewers told the panel the device "may do more harm than good." However, the company said it hasn't heard from the FDA since then.

ROCHE

- **Rituxan (rituximab) –** A study published in the ***Archives of Neurology*** found that when used in rheumatoid arthritis, Rituxan has a "modest" risk of progressive multifocal leukoencephalopathy (PML), ~1 in 25,000 patients, which is a far lower rate than occurs with **Biogen Idec/Elan**'s Tysabri (natalizumab) in multiple sclerosis patients.
- **ROCHE and PLEXXIKON's vemurafenib (RG-7204, PLX-4032)** was submitted to both the FDA and the European Medicines Agency (EMA) to treat BRAF V600 mutation-positive metastatic melanoma. Roche also submitted a companion cobas BRAF V600 diagnostic test to identify eligible patients.

WARNER-CHILCOTT's Atelvia (risedronate delayed-release) – FDA issues warning letter

The FDA sent the company a warning letter saying a video on YouTube for this osteoporosis treatment is misleading, makes unsubstantiated claims, doesn't properly discuss risks, and was not pre-approved by the FDA as required. The FDA's Division of Drug Marketing, Advertising, and Communications (DDMAC) now wants to review all the company's marketing materials.

REGULATORY NEWS

Affordable Medicines Caucus

Rep. Jo Ann Emerson (R-MO) and Rep. Peter Welch (D-VT) have started a bipartisan Affordable Medicines Caucus in Congress to promote the use of generic and biotech drugs that are – surprise – affordable. The legislators said they will focus on increasing funding for generic drug reviews at the FDA and drafting legislative proposals to widen use of generics, including by Medicaid and Medicare. Access to biotech medications will also be a focus, particularly finding ways to make them available to people who can't afford high copays.

FDA drug approvals to be up for 2011

Janet Woodcock, MD, director of the FDA's Center for Drug Evaluation and Research (CDER), predicted FDA drug approvals in 2011 may "slightly" outpace 2010. She denied the FDA is making it more difficult for companies to gain approval of new drugs, saying the Agency only strengthened the process as the science has required it. Dr. Woodcock also said the FDA is finding it increasingly difficult to find experts for its advisory committees who are not also hired by pharmaceutical companies as consultants or speakers.

FDA moving ahead on biosimilars

The FDA will issue general guidance this year on what generic versions of biosimilar biotechnology drugs will have to do to get approved. Dr. Woodcock said the FDA hasn't received any biosimilar applications but added, "We are open for business right now…We are very interested in providing competition where we have a mandate."

Dr. Woodcock said the FDA is meeting with companies – traditional generic manufacturers, brand biotech companies, and firms new to the U.S. market – individually and giving them advice on their programs, adding:

- Human testing will not be an across-the-board requirement.
- Longer-lasting versions of existing biotech drugs – or changes that make an existing biotech drug safer or more effective – would be considered a new molecule, with a new 12-year exclusivity.
- The FDA learned from the European experience that the Agency needs to be able to track down the specific manufacturer of a biosimilar drug.

The FDA also plans to frontload the charges for biosimilar reviews, but the reviews won't be cheaper than for original brand biotech drugs. The FDA has not finalized the fee system for biosimilars yet and is seeking public comment through June 9, 2011, on its proposed fee schedule, which is very similar to new drugs (with a basic ~$150,000 IND application fee). The FDA also will hold meetings with the public, industry, and other stakeholders later this year.

Iceland changes device oversight

Medical devices used to be handled by the Directorate of Health in Iceland, but responsibility for devices was transferred to the Icelandic Medicines Agency (IMA) on May 1, 2011.

European regulatory approvals

- **TECHNOLAS PERFECT VISION's SUPRACOR**, a laser treatment for presbyopia, has received CE mark approval and is now commercially available.

Recent FDA approvals and clearances

- **BRAINLAB's HybridArc radiosurgery planning software** received 510(k) clearance for use with Linac treatment systems.
- **MERCK's Victrelis (boceprevir)** is the first direct-acting antiviral to be approved by the FDA. It was approved to treat chronic hepatitis C (HCV) in both naïve and treatment-failure patients in combination with pegylated interferon + ribavirin. The FDA approved response-guided therapy. Patients are instructed to take Victrelis three times a day with a snack or a meal.
- **MERIDIAN BIOSCIENCE's Premier C. difficile GDH test** received 510(k) clearance. It is designed to distinguish between toxigenic and non-toxigenic forms of *C. diff* in patients with diarrhea. The test already has a CE Mark.
- **SANOFI PASTEUR's Fluzone Intradermal** – for people age 18-64. It is expected to be available for the 2011-12 flu season.

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
	May 2011	
May 17-18	**PK, safety, and efficacy data plus OTC dosing information and pediatric labeling** for acetaminophen	Joint meeting of the FDA's Non-Prescription Drugs Advisory Committee and Pediatric Advisory Committee
May 19	Discussion of ACCORD Lipid trial as it relates to **Abbott Labs' Trilipix** (fenofibric acid)	FDA's Endocrinologic and Metabolic Drugs Advisory Committee
May 23	**Vertex Pharmaceuticals' telaprevir**, a treatment for hepatitis C	PDUFA date
May 29	**Roche/Genentech's Lucentis** (ranibizumab) – results of Phase III trial	EURETINA Congress in London
May 30	**Optimer Pharmaceuticals' fidaxomicin** for the treatment of *C. diff*	PDUFA date
	June 2011	
June 2-3	Approaches and endpoints for devices for **seizure detection, cognitive evaluation, and traumatic brain injury/concussion assessment**	Joint workshop of the FDA, the American Academy of Neurology, the American Epilepsy Society, and the National Academy of Neuropsychology
June 8-9	**Reprocessing medical devices**	FDA public workshop
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 20	**Salix Pharmaceuticals' Xifaxan** (rifaximin) for non-constipation IBS	Company to meet with FDA on complete response letter
June 23	**Pfizer/King Pharmaceuticals/Pain Therapeutics' Remoxy** (tamper-resistant oxycodone CR) for pain	PDUFA date
June 23-24	**HCV drug development**	Workshop on Clinical Pharmacology of Hepatitis Therapy, Boston
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)
June 29	**Cellular and gene therapy products** for retinal disorders	FDA's Cellular Tissue and Gene Therapies Advisory Committee
	Other 2011 meetings/events	
July 11	**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 20	**Regeneron's afilbercept** (VEGF Trap-Eye) for AMD	PDUFA date
August 25	**Shire's Firazyr** (icatibant) for hereditary angioedema	PDUFA date
August 30	**Seattle Genetics and Takeda's brentuximab vedotin** for two orphan indications – refractory Hodgkin's lymphoma and anaplastic large cell lymphoma (ALCL)	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
December	**Allergan's brimonidine tartrate intravitreal implant** – Phase II trial in dry AMD to complete	Company announcement or medical conference presentation
December 8	**Antares Pharma's Anturol Gel** (oxybutinin gel), a treatment for overactive bladder	PDUFA date
	2012 meetings/events	
February 2012	**Alcon's tandospirone** for dry AMD – Phase III final data expected	Company announcement or medical conference presentation