TRENDS-in-MEDICINE

July 3, 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

- **ABIOMED's Impella Recover LP 2.5 –** The FDA sent the company a warning letter ordering it to stop promoting this percutaneous left ventricular assist device for off-label uses.
- **ALLERGAN's Botox (onabotulinumtoxinA) –** Doctors at Monash Medical Center in Australia plan to test Botox as a therapy for severe asthma by injecting the toxin to relax muscle spasms that may be causing patients difficulty breathing. The study is being undertaken because a survey found ~50% of severe asthmatics have problems with their voiceboxes as well as their lungs, problems that are similar to vocal cord dysphonia, for which Botox is frequently used.
- **AMGEN's Vectibix (panitumumab) –** The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) reversed itself and is now endorsing Vectibix with chemotherapy as first- or second-line therapy for metastatic colorectal cancer.
- **ANACOR PHARMACEUTICALS' AN-2728 –** The company announced positive results from a 12-week Phase II trial in mild-to-moderate psoriasis, with psoriasis plaques reduced 26% after 6 weeks. However, this wasn't an efficacy trial, and the statistical value of the findings was not reported.
- **APPLIED MEDICAL TECHNOLOGY** received a warning letter from the FDA over manufacturing problems at its Ohio plant.
- **APRICUS BIOSCIENCES' Vitaros (alprostadil),** an erectile dysfunction drug, was accepted by European regulators, who are expected to make a decision by February 2012. Vitaros is approved in Canada, and the company plans to launch there in 2H11.
- **ARCHIMEDES PHARMA's Lazanda (intranasal fentanyl pectin),** a nasal spray marketed in some Europen countries as PecFent, was approved by the FDA for management of breakthrough pain in cancer patients.
- **CARDIUM THERAPEUTICS** is acquiring most of the assets of **Transdel Pharmaceuticals**, which filed for bankruptcy after running out of money needed to conduct a second Phase III trial of transdermal Ketotransdel (ketoprofen).
- **CYNOSURE** acquired the assets of an aesthetic laser company, **Hoya ConBio** (a wholly owned subsidiary of Japan-based Hoya Corp.), which has >3,200 laser systems installed worldwide.

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- **ENDO PHARMACEUTICALS' Endocet (10 mg oxycodone/325 mg acetaminophen)** – Two lots of this painkiller were recalled after some 100-pill bottles were found to contain a different dose (10 mg/650 mg), which are a different size and shape and have different markings.

- **FOREST LABORATORIES and ALMIRALL's aclidinium bromide**, an inhaled, long-acting antimuscarinic for chronic obstructive pulmonary disease (COPD), was resubmitted to the FDA for approval at a dose of 400 µg BID. In 2009, the FDA turned the drug down, asking for data on more frequent and higher dosing. The companies withdrew their QD dosing application in Europe in January 2011.

- **LUNDBECK's Nembutal (pentobarbital)**, an anesthetic used in lethal injections, will stay on the U.S. market as a seizure medication, but the company will only ship it to U.S. distributors and pharmacies that agree, in writing, not to sell the drug to prisons in states where the drug may be used in executions.

- **NOVARTIS' glycopyrronium bromide (NVA237)** given once daily significantly improved lung function in patients with moderate-to-severe COPD vs. placebo in a Phase III trial, showing similar efficacy to **Pfizer's Spiriva** (tiotropium).

- **OPTO CIRCUITS' Powerheart G3** automated external defibrillators were cleared by Japanese regulators for marketing in that country.

- **PHILIPS HEALTHCARE** is buying most of **Sectra**'s mammography division. Sectra said it wants to focus on developing its medical imaging IT business and other portfolios.

- **Rapamycin** – Researchers reported this mTOR inhibitor clears the protein progerin from cells of children suffering from progeria, a rare genetic condition (also known as Hutchinson-Gilford progeria syndrome) in which aging occurs at a hyper rate. National Institutes of Health (NIH) director Francis Collins, MD, PhD, said the rodent findings may have implications for understanding the aging process.

- **SHIRE's Replagal (agalsidase alfa)** – The company's Massachusetts plant was given the green light by the FDA to produce this enzyme-replacement treatment for Fabry disease, which will boost the company's manufacturing flexibility and help end shortages.

- **Valproate products** – The FDA warned doctors that children born to mothers who take the antiseizure medications valproate sodium, valproic acid, or divalproex sodium – e.g., **Abbott's Depakote** and **Noven Therapeutics' Stavzor** – during pregnancy have an increased risk of lower cognitive test scores than children exposed to other antiseizure medications during pregnancy. The FDA is advising that doctors counsel women of childbearing age about the potential risks of this and other adverse events and consider less risky alternatives.

- **VIVUS' avanafil**, a drug to treat erectile dysfunction, was submitted to the FDA for approval. The PDUFA date is about April 30, 2012.

NEWS IN BRIEF

ABBOTT and REATA PHARMACEUTICALS' bardoxolone – positive Phase II results published

A 227-patient Phase II study – published in the ***New England Journal of Medicine*** and simultaneously presented at the European Renal Association-European Dialysis and Transplant Association Congress in Prague – found bardoxolone reversed the decline in kidney function in patients with chronic kidney disease (CKD). A Phase III trial began recently, with results due in 2013. The trial tested three QD doses of bardoxolone: 25 mg, 75 mg, and 150 mg vs. placebo. After six months, the drug significantly increased the glomerular filtration rate (GFR).

ASTRAZENECA's Brilinta/Brilique (ticagrelor)

- **Mixed trial results.** Patients adding Brilinta to >300 mg of aspirin did worse than patients adding Brilinta to **Sanofi's Plavix** (clopidogrel), a new analysis of the PLATO trial found. However, patients taking Brilinta + low-dose aspirin had fewer heart attacks, strokes, and early death than patients on Brilinta + Plavix.

- **NICE endorses.** This anticoagulant received a preliminary positive recommendation from the U.K.'s National Institute for Health and Clinical Excellence (NICE), which said it is cost-effective for the National Health Service (NHS) to use in adults with acute coronary syndrome. A final decision is expected by the end of the year. The FDA PDUFA date is July 20, 2011.

DENDREON's Provenge (sipuleucel-T)

- **Reimbursement.** The Centers for Medicare and Medicaid Services (CMS) decided to fully cover this prostate cancer immunotherapy for on-label, but not off-label use, calling it a "reasonable and necessary" treatment despite its $93,000-per-course price tag.

- **Supply.** The FDA cleared the company's second plant, the one in Los Angeles, to make Provenge. A third plant in New Jersey is still waiting for clearance.

E-prescribing – no better than written prescriptions

A study published in the ***Journal of the American Medical Informatics Association*** found that up to 12% of e-prescriptions sent to pharmacies contain errors, which isn't any better than handwritten prescriptions. Researchers analyzed 3,850 computer-generated prescriptions written over a 4-week period and found 452 had errors, including 163 potentially harmful mistakes. No errors were rated life-threatening. The drugs most commonly associated with mistakes were nervous system drugs (27%), cardiovascular drugs (13.5%), and anti-inflammatories/antibiotics (12.3%).

GILEAD SCIENCES

- **Johnson & Johnson's Tibotec division** and Gilead plan to work together to develop two combination HIV treatments: one combining J&J's **Prezista** (darunavir) boosted by Gilead's **cobicistat** and another combining Prezista + Gilead's **Emtriva** (emtricitabine) + Gilead's **GS-7340**.
- **Truvada (tenofovir + emtricitabine)** – A group of 55 healthcare providers sent the FDA a letter asking the Agency not to approve Truvada for HIV prevention, saying approval of Truvada as a pre-exposure prophylactic could contribute to the spread of HIV and drug resistance.

JOHNSON & JOHNSON

- **Weekly recall.** More **Tylenol** (acetaminophen) this time, again because of the "uncharacteristic" musty odor that has plagued this and other products. *When will J&J resolve this?*
- **Xarelto (rivaroxaban).** The FDA approved a 10 mg QD dose of this oral Factor Xa inhibitor for prevention of deep vein thrombosis (DVT) in patients for 35 days following hip replacement surgery and for 12 days following knee replacement.

MEDTRONIC's Infuse (rhBMP-2) – controversy deepens

The Spine Journal devoted an entire issue to the topic of researchers not reporting negative results with this spine surgery bone-fusion enhancer in published articles. And a new analysis of FDA documents and other sources suggested ≤50% of Infuse patients may have an adverse event. Eugene Carragee, MD, editor of ***The Spine Journal***, and colleagues said this means adverse events are 10-50 times more frequent than the original estimates, and they promised new publication guidelines for their journal.

PFIZER

- **Axitinib** – This small molecule tyrosine kinase inhibitor was submitted to the FDA to treat advanced renal cell carcinoma in patients refractory to other therapies. The PDUFA date is about February 28, 2012. The drug was submitted to European regulators last month.
- **Neurontin (gabapentin)** – A review in the ***Archives of Internal Medicine*** called a 1999 Phase IV study of this epilepsy drug, STEPS, which was sponsored by Parke-Davis (now Pfizer), a marketing gimmick – a "seeding trial" designed to boost prescriptions. The author of an accompanying commentary urged clinicians, researchers, and institutional policymakers to more closely scrutinize postmarketing studies.
- **Russia** – Pfizer plans to work with a second Russian venture capital company, **ChemRar**, to research and market new drugs and vaccines in Russia and surrounding countries – particularly cardiac, metabolic, infectious disease, and cancer drugs.

ROCHE/GENENTECH

- **Avastin (bevacizumab)** – An FDA panel was convened to hear Genentech's appeal of the FDA's decision to withdraw the approval for Avastin in metastatic breast cancer because confirmatory trials failed to demonstrate a clinical benefit, and the panel voted unanimously (6-0) that the FDA action was correct. The panel also said the indication should not be allowed to continue while Genentech runs a new confirmatory trial. (See the coming ***Trends-in-Medicine*** report for more details.)
- **Collaborating with Evotec** on novel protein-activity-based biomarkers for Roche's oncology drugs under development.

REGULATORY NEWS

FDA urged to screen API suppliers

Sen. Sherrod Brown (D-OH) wrote the FDA asking the Agency to more closely scrutinize drugmakers that purchase active pharmaceutical ingredients (APIs) from countries with lower safety standards. A recent report found that >80% of APIs are produced at foreign plants, and most of those are not carefully inspected by the FDA.

Recent FDA approvals

GE's Optima XR220amx, **Optima XR200amx**, and **Brivo XR285amx**, new mobile x-ray systems

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
	July 2011	
July 11	**Novartis' Arcapta Neohaler** (indacaterol) long-acting beta agonist (LABA) for COPD	PDUFA date
July 14	**Seattle Genetics' brentuximab vedotin** to treat both relapse/refractory Hodgkin's lymphoma and relapsed/refractory systemic anaplastic large cell lymphoma	FDA's Oncologic Drugs Advisory Committee
July 19	**Bristol-Myers Squibb and AstraZeneca's dapagliflozin,** the first SGLT2 inhibitor for Type 2 diabetes	FDA's Endocrinologic and Metabolic Drugs Advisory Committee
July 20	**Edwards Lifesciences' Sapien** percutaneous aortic valve	FDA's Circulatory System Advisory Committee
July 20	**AstraZeneca's Brilinta** (ticagrelor), an anticoagulant	PDUFA date
July 21	A humanitarian device exemption for **Berlin Heart's EXCOR pediatric ventricular assist device (VAD)** as a bridge-to-transplant	Circulatory Systems Devices Advisory Committee
	August 2011	
August 12	**Physician-owned distributorships (PODs)**	Inspector General initial report due to Senate Finance Committee
August 20	**Regeneron's aflibercept** (VEGF Trap-Eye) for wet AMD	PDUFA date
August 25	**Shire's Firazyr** (icatibant injection) 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
	Other 2011 meetings/events	
Summer	Report on **FDA 510(k) reform**	Institute of Medicine
2H11	**Abbott's RX Acculink** carotid stent	FDA final decision expected
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 28	**Pacira Pharmaceuticals' Exparel** (bupivacaine extended-release liposome injection), a painkiller	PDUFA date
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
December 13	**Endo Pharmaceuticals' Opana** (extended-release oxymorphone), a painkiller	PDUFA date
	2012 meetings/events	
February	**Alcon's tandospirone** for dry AMD – Phase III final data expected	Company announcement or medical conference presentation
February 17	**Corcept Therapeutics' Corlux** (mifepristone) for Cushing's syndrome	PDUFA date
February 28	**Pfizer's axitinib** for advanced renal cell carcinoma	PDUFA date (*approximate*)
April 30	**Vivus' avanafil** for erectile dysfunction	PDUFA date (*approximate*)