TRENDS-in-MEDICINE

June 26, 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

- **ACCENTIA BIOPHARMACEUTICALS' Revimmune**, an investigational therapy for multiple sclerosis (MS), was granted orphan drug status by the FDA.
- **AMYLIN and LILLY and ALKERMES' Bydureon (weekly exenatide)** was approved by European regulators. In 2010, the FDA rejected Bydureon, asking for more data.
- **Antipsychotics –** Under new rules implemented this month, children under 3 on Medicaid in Texas will not be prescribed antipsychotics without special authorization.
- **ASTRAZENECA's Brilinta (ticagrelor)**, an oral antiplatelet agent, was approved by Health Canada to prevent cardiovascular death, heart attack, or stroke in patients with acute coronary syndromes (ACS).
- **BIOGEN IDEC and ELAN's Tysabri (natalizumab) –** European regulators approved expanded labeling for this MS antibody treatment, which cites anti-JC virus antibody positivity as a risk factor for progressive multifocal leukoencephalopathy (PML) and warns that the patients at greatest risk of PML are those who are JCV+, used Tysabri for >2 years, and had prior immunosuppressant therapy.
- **CSL BIOTHERAPIES' Fluvax –** The company got a warning letter from the FDA that its manufacturing process for this flu vaccine didn't meet good manufacturing practice requirements. Problems included failure to investigate unexplained discrepancies between batches and failure to establish and follow written production and process controls. Last year, Australian authorities withdrew CSL's flu vaccine from use in children under age 5 after 23 Australian children were hospitalized with convulsions and high fevers after post-Fluvax.
- **ENDO PHARMACEUTICALS' Opana (extended-release oxymorphone) –** The FDA accepted the resubmission of the tamper-resistant formulation of this painkiller, which the FDA had rejected in January 2011 asking for additional risk management data or more information on its crush-resistant properties. The new PDUFA date is December 13, 2011.
- **FIBROCELL SCIENCE's Laviv (azfibrocel-T)**, an injectable wrinkle treatment that uses a patient's own cells to restore elasticity to the skin, was approved by the FDA. Doctors take a sample of fibroblasts from behind a patient's ear and send them to the company, where they are expanded in a cell culture over 11-22 weeks and then sent back to the doctor for injection into nasolabial folds.

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- **Generic drugs** – A 5-4 Supreme Court decision means generic drugmakers will be shielded from failure-to-warn lawsuits as long as their product labels are identical to those of the brand product.
- **GLAXOSMITHKLINE's Augmentin (amoxicillin and clavulanate potassium suspension)** – GSK was ordered by the Chinese government to recall this pediatric antibiotic because it was found to be tainted with a plasticizer, diisodecyl phthalate (DIDP). Previously, Hong Kong ordered a recall of Augmentin (made at a French factory) after tests showed it had an unsafe level of DIDP.
- **LIFECYCLE PHARMA's LCP-Tacro** – The company said a study showed this once-daily drug worked as well as **Astellas Pharma**'s twice-daily Prograf (tacrolimus) in preventing organ rejection in kidney transplant patients. The company plans to file for U.S. and European approvals in 1Q13, after completion of another ongoing trial.
- **Pfizer/King Pharmaceuticals' Remoxy (tamper-resistant oxycodone)** – The FDA rejected this painkiller, issuing a Complete Response Letter. The FDA had turned down a previous version of Remoxy in 2008, but Pfizer resubmitted it in January 2011. Pfizer did not provide details on what concerns the FDA expressed in the letter.
- **Prescription data mining** – A 6-3 Supreme Court decision struck down a law in Vermont that restricted the collection and sale of prescription-drug data.
- **Prostate cancer research** may take a hit. The House Appropriations Committee passed a bill that would cut funding for the Department of Defense Prostate Cancer Research Program by 20% (from $80 million to $64 million) in fiscal year 2012.
- **PROSTRAKAN GROUP's Rectiv (nitroglycerin ointment 0.4%)** was approved by the FDA for the treatment of moderate-to-severe pain associated with chronic anal fissures, making it the only FDA-approved product for this condition. The company plans to launch Rectiv in 1Q12.
- **REPLIGEN's RG-3039**, a treatment for spinal muscular atrophy, received FDA fast track designation and a positive opinion for orphan drug status in Europe.
- **SANOFI** and pharmacy benefits manager **Medco Health Solutions/United BioSource** will work together in a multiyear collaboration to design drug and device studies, collect information, and do research. Sanofi hopes to identify groups of patients who are in need of new treatments, determine patient populations in which the drugs are most effective, compare new drugs to current therapies, and make sure the treatments are used in an effective way.
- **SHIRE's Firazyr (icatibant)** – The FDA's Pulmonary-Allergy Drugs Advisory Committee voted 12-1 that this treatment for hereditary angioedema is safe and effective and appropriate for patients to inject in themselves. The PDUFA date is August 25, 2011.
- **ST. JUDE MEDICAL's Fortify and Unify** – The Japanese Ministry of Health, Labor, and Welfare gave St. Jude permission to market the Fortify implantable cardioverter defibrillator (ICD) and the Unify cardiac resynchronization therapy defibrillator (CRT-D).
- **SYNAGEVA BIOPHARMA's SBC-102**, an enzyme-replacement therapy for lysosomal acid lipase deficiency, received fast track designation from the FDA. It already has orphan drug status in both the U.S. and Europe.
- **TAKEDA PHARMACEUTICALS' Actos (pioglitazone)** – The European Medicines Agency (EMA) said it will delay a decision on whether this diabetes drug should remain on the market or not due to a possible link to bladder cancer. A final decision is expected at the EMA's meeting next month.
- **UNITED THERAPEUTICS** licensed a potential lung disease treatment from **Pluristem Therapeutics** to treat pulmonary arterial hypertension. United Therapeutics got the development and marketing rights, but Pluristem, which develops therapies using placental cells, will manufacture it.

NEWS IN BRIEF

Alzheimer's disease – new biomarker identified

A study of 58 patients with mild cognitive impairment (MCI), published in ***Neurology***, suggested soluble amyloid precursor protein beta (sAPPβ) in spinal fluid may be a more accurate biomarker for Alzheimer's disease than the currently established biomarkers. The researchers found that MCI patients who developed Alzheimer's disease had significantly higher levels of sAPPβ than those who did not develop Alzheimer's disease (1,200 ng/ml vs. 932 ng/ml).

The researchers found the best predictor of Alzheimer's disease development was a combination of sAPPβ, tau protein (an established marker of brain cell damage), and age. When these three factors were combined, the results were ~80% accurate in progression to Alzheimer's. Amyloid beta1-42, or Aβ1-42, which previously was considered a biomarker for Alzheimer's disease, was not a predictive factor in this study.

BRISTOL-MYERS SQUIBB's Eliquis (apixaban)

- **Approved in Europe.** Apixaban was approved by European regulators for the prevention of venous thrombo-embolic events (VTE) in adults who have undergone elective hip or knee replacement surgery.
- **Beats warfarin in AFib trial.** The company released the topline results from the ARISTOTLE trial, showing this twice-daily, oral Factor Xa inhibitor was superior to warfarin on both efficacy and safety (major bleeding) for the prevention of stroke in patients with atrial fibrillation. In comparison, the key competitor, **Johnson & Johnson** and **Bayer**'s once-daily Xarelto (rivaroxaban), was non-inferior but not superior to warfarin in an intent-to-treat analysis of a similar trial, ROCKET-AF. The full ARISTOTLE data will be presented at the European Society of Cardiology (ESC) meeting August 28, 2011.

Cancer vaccine – new approach to immunotherapy

In a study published in ***Nature Medicine***, researchers reported on a new approach to cancer immunotherapy using a library of DNA taken from organs in which tumors can form. The British and U.K. researchers successfully tested the vaccine in mice with prostate cancer, but it has potential against skin and breast cancer as well. This is still several years away from testing in humans, but it is a step forward.

JOHNSON & JOHNSON

- **Recalls aren't over.** The latest problem: **Risperdal** (risperidone). J&J/Ortho-McNeil-Janssen Pharmaceuticals recalled this antipsychotic (both brand and generic products) due to an odor blamed on a chemical preservative, 2,4,6-tribromoanisole, used in wood shipping pallets.
- **Velcade (bortezomib)** – The U.K.'s National Institute for Health and Clinical Excellence (NICE) rejected J&J's appeal of its decision to support use of Celgene's Thalomid (thalidomide) instead of Velcade for multiple myeloma. Velcade may only be used by patients who can't tolerate thalidomide.

MEDICIS' Dysport beats ALLERGAN's Botox

In a 30-day, 90-patient, head-to-head study published in the ***Archives of Facial Plastic Surgery***, Dysport (abobotulinumtoxinA) was injected in one side of the face and Botox (onabotulinumtoxinA) in the other, giving a same-patient comparison. The result: moderate-to-severe lateral orbital rhytids (crow's feet) responded significantly better to 30 U Dysport than to 10 U Botox.

The primary endpoint was improvement in the 5-point Merz photographic scale, and investigator-assessed efficacy at maximal contraction was 2.60 for Dysport and 2.33 for Botox ($p=0.01$). Patient-assessed efficacy at maximal contraction was 2.34 for Dysport and 2.13 for Botox ($p=0.03$). Patients as well as physicians rated the results with Dysport superior to those of Botox. In fact, twice as many patients favored the Dysport-treated side of the face (67% vs. 33%, $p=0.002$). However, the researchers said the findings do not support a superiority claim for other regions of the face or groups of facial muscles. And there was no significant difference in the mean Merz score at rest.

The researchers requested funding from both Medicis and Allergan, but only Medicis provided funding.

MEDTRONIC's Infuse (BMP-2) – Senate investigation

Citing news reports based on a ***Milwaukee Journal Sentinel/ MedPage Today*** investigation, the Senate Finance Committee launched an investigation into reports that doctors with financial ties to Medtronic knew about potentially serious complications with this spine surgery fusion augmentation device but did not report those problems – cancer, ectopic bone formation, cervical swelling, and male retrograde ejaculation (which can lead to sterility) – in journal articles.

MERCK KGAA's cladribine – abandoned in MS

Deciding it would just take too long to meet regulatory requirements, the company has given up efforts to get this oral immunosuppressant approved to treat for multiple sclerosis. Both the FDA and European regulators wanted more data, which would require a new trial. Merck is withdrawing cladribine as an MS treatment in Australia and Russia, where it was approved. However, Merck does plan to continue the three ongoing cladribine MS trials, CLARITY extension, ORACLE MS, and ONWARD.

NOVARTIS' Ilaris (canakinumab) – FDA panel rejected gout indication

The FDA's Arthritis Advisory Committee voted 11-1 against recommending approval of this gout therapy. The panel agreed Ilaris is effective in extending the time between flares and in reducing the frequency of further attacks but decided the safety concerns – particularly serious infections – outweigh the benefits in gout. Ilaris already is approved to treat cryopyrin-associated periodic syndrome (CAPS) in adults and children. Novartis is not giving up on gout and plans to work with the FDA to try to identify a subgroup of patients who might benefit.

ROCHE and CURIS' vismodegib – positive mid-stage results

A pivotal Phase II study found this oral Hedgehog pathway inhibitor met the primary endpoint, shrinking tumors and healing lesions in people with advanced basal cell carcinoma (BCC) for whom surgery was considered inappropriate. The results of ERIVANCE BCC, an international, multicenter, single-arm, two-cohort, open-label trial, were presented at the European Association of Dermato-Oncology (EADO) Congress in Nantes, France. They showed that vismodegib 150 mg QD led to:

- An overall response rate (the primary endpoint) of 43% in patients with locally advanced BCC and 30% in patients with metastatic BCC by independent review.
- A clinical benefit rate (response + prolonged stable disease >24 weeks) of 75%.
- Median PFS of 9.5 months for both types of BCC.
- The most common adverse events were muscle spasms, hair loss, dysgeusia, weight loss, fatigue, decreased appetite, nausea, and diarrhea. Serious adverse events occurred in 25% of patients, but only 4% were deemed treatment-related. There were 7 deaths, which were not considered related.

Statins – another warning about high doses

Earlier this month, the FDA issued a warning about myopathy with high-dose (80 mg) simvastatin. Now, a meta-analysis of five trials with a total of 32,752 patients, published in the ***Journal of the American Medical Association***, found all high-dose statin therapies raise the risk of new-onset diabetes in a dose-dependent manner. For example, 80 mg simvastatin and 80 mg **Lipitor** (**Pfizer, atorvastatin**) increased the risk of diabetes by 12% vs. a 10 mg to 20 mg dose of the same drugs or vs. 40 mg pravastatin, which translates to a 20% overall increased risk of diabetes for high-dose statin users.

Overall, the researchers concluded there is one new case of diabetes for every 498 patients treated with high-dose statins, but one cardiovascular event was prevented for every 155 patients treated. Thus, the researchers said the cardiovascular benefits still outweigh the diabetes risk, preventing 6.5 cardiovascular events per 1,000 patient-years vs. causing 2.0 cases of diabetes.

Tonsillectomy technologies – all but one new approach found ineffective

A meta-analysis of 33 trials with a total of 3,139 patients, published in ***Archives of Otolaryngology – Head & Neck Surgery***, found no benefit with radiofrequency ablation (**ArthroCare**'s **Coblation**) or with **Johnson & Johnson**'s ultrasound **Harmonic Scalpel** vs. conventional cold steel and/or electrocautery dissection. However, the U.K. researchers found vessel sealing systems such as **LigaSure**'s system did have significant advantages in terms of operative time (~4 minutes less, $p=0.02$), perioperative and postoperative bleeding ($p \leq 0.004$), and pain ($p \leq 0.01$).

Patients treated with the Harmonic Scalpel had less perioperative bleeding, but this was the only significantly different outcome, and the researchers noted this endpoint "does not have any measurable clinical significance."

REGULATORY NEWS

Australia and New Zealand form oversight agency

The governments of Australia and New Zealand are setting up the Australia New Zealand Therapeutic Products Agency, a joint agency that will regulate and ensure the safety of medical devices, drugs, and other treatments in both countries. The new agency will replace Australia's Therapeutic Goods Administration and New Zealand's Medical Devices Safety Authority.

CMS: legislation to allow drug price negotiating

A bipartisan bill was introduced in the House of Representatives, co-sponsored by Rep. Jo Ann Emerson (R-MO) and Rep. Peter Welch (D-VT), that would require CMS to negotiate lower prescription drug prices for Medicare. Not surprisingly, the pharmaceutical industry opposes the legislation.

FDA inadequately monitors device recalls

The Government Accountability Office (GAO) report released by Sen. Chuck Grassley (R-IA) and Sen. Herb Kohl (D-WI) found the FDA doesn't assess whether medical device recalls are successful. The GAO said the FDA doesn't have clear policies in place to determine whether a recall worked, doesn't analyze individual recalls in search of more fundamental problems, doesn't document its reasons for determining the recalls are complete, and doesn't have criteria to measure whether manufacturers actually pull every defective device during a recall.

The GAO report noted, "If unaddressed by FDA, the combined effect of these gaps may increase the risk that unsafe medical devices could remain on the market." Sen. Grassley added, "It looks like the FDA is missing an opportunity to proactively identify and address risks presented by unsafe devices."

FDA issues guidance on artificial pancreas systems

Hoping to advance development of an artificial pancreas – an automated, closed-loop system combining a continuous glucose monitor, an insulin infusion pump, and a glucose meter – for Type 1 diabetics, the FDA issued draft guidance for a Low Glucose Suspend system, an early version of artificial pancreas. A Low Glucose Suspend system can help reduce/lessen the severity of hypoglycemic events by temporarily reducing/stopping insulin delivery, but patients still must use a glucose meter and inject insulin.

The FDA is seeking input on the types of clinical studies that should be conducted and what their target outcomes should be to demonstrate safety and effectiveness. The FDA also is working on a second draft guidance for more autonomous artificial pancreas systems, which is expected to be issued by the end of the year.

FDA may change required drug ad information

The FDA is considering a change in the drug information required in ads to a brief summary format similar to the "Drug Facts" design used for over-the-counter products after a study showed the shorter format had better comprehension.

In a study published in ***Medical Decision Making***, the FDA's Division of Drug Marketing, Advertising, and Communications (DDMAC) reported on its test of ads for a bogus weight-loss drug in 300 adult, overweight mall-shoppers, using four different brief summary formats – Drug Facts, Q&A, highlights, and traditional. The Drug Facts format was the clear winner, both in terms of comprehension and mastery of information.

However, the Drug Facts format was the shortest, and DDMAC concluded the test results "do not lead unequivocally to this format…The results do demonstrate that improvement over the traditional brief summary format is possible."

FDA accused of slow device approvals

A report by Emergo Group found the FDA took an average of 132 days to clear medical devices through the 510(k) process in 2010, up from an average of 96 days in 2006. Chris Schorre, Emergo's vice president for global marketing, suggested one possible explanation: "FDA reviewers are requesting more clinical performance data from a higher percentage of manufacturers submitting 510(k) applications."

FDA warning letters

- **ARTSANA S.P.A.'s sterile insulin syringes and pen needles** – The FDA found problems with the company's complaint handling and record keeping at this Italian company's plant, and the company's response appears to be inadequate.
- **POINTCARE TECHNOLOGIES' hematology *in vitro* diagnostic products** – An inspection found problems with manufacturing, including issues with osmolality and optical density. The FDA found the company's response inadequate.

FDA recalls

- **BECKMAN COULTER's Synchron *in vitro* test** – because of reports of incorrect electrolyte results due to maintenance-related hardware issues.
- **BECTON DICKINSON's BD Nokor Admix Needle 16** for use in aspiration of medications in the pharmacy – because of incorrect unit package labels.
- **BIOMET's RingLoc + Acetabular Shells and Regenerex RingLoc + Solid Acetabular Cups** – after an investigation found the locking ring may be assembled incorrectly in the acetabular shell and the liner cannot be completely seated in the shell.
- **BIOSITE's Cholestech LDX Lipid Profile test cassettes** – due to a calibration issue.
- **CHURCHILL MEDICAL SYSTEMS' AMS-7080CP Dressing Change Kit** – due to potential bacterial contamination.
- **COREPHARMA's ropinirole HCl** – due to an obsolete version of the package insert.
- **JOHNSON & JOHNSON/DEPUY's Confidence Diamond Tip Introducer Needle** – because packages were mislabeled.
- **JUBILANT CADISTA PHARMACEUTICALS' methylprednisolone** – because it may contain partially eroded or low-weight tablets.
- **LUITPOLD PHARMACEUTICALS' Methyldopate HCl injection** – due to particulate matter in some vials.
- **Optical Guidance Platform, versions 2.6 and 2.6.1** – due to an anomaly that can cause the software not to display the correct transfer data on the patient file.
- **PHARMACEUTICAL ASSOCIATES' lactulose** – due to package deviations that could have compromised the integrity of the product.
- **PHILIPS HEALTHCARE's Philips SureSigns VM Series Patient Monitors and SureSigns VS3 Vital Signs Monitors** – because of speaker malfunction messages.

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
	June	
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
	July	
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	
August 12	**Physician-owned distributorships (PODs)**	Inspector General initial report due to Senate Finance Committee
August 20	**Regeneron Pharmaceuticals' Eylea** (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 2012	**Alcon's tandospirone** for dry AMD – Phase III final data expected	Company announcement or medical conference presentation