TRENDS-in-MEDICINE

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Quick Takes

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

SHORT TAKES

- **ACTAVIS's Fentanyl Transdermal System** – These pain patches were recalled because they might release more than the intended 25 µg per hour of the opioid. No adverse events in patients have been reported. Customers are being asked to return the patches to the company.
- **ALLOS THERAPEUTICS' Folotyn (pralatrexate injection)**, a lymphoma therapy, received an additional orphan drug designation from European regulators as a treatment for Hodgkin's disease.
- **BLUE CROSS/BLUE SHIELD OF MICHIGAN** – The U.S. Justice Department has filed an antitrust lawsuit against Blue Cross/Blue Shield of Michigan alleging the insurer's contracting tactics with hospitals have led to higher prices and fewer choices for health coverage in the state.
- **CARDIOME PHARMA/ASTELLAS' Kynapid (vernakalant hydrochloride)** – Enrollment was suspended in a Phase III trial of this injectable atrial fibrillation treatment after one patient experienced cardiogenic shock, a potentially fatal heart problem, and required resuscitation and aggressive intervention.
- **GENERAL ELECTRIC** is buying **Clarient**, which has molecular diagnostics technology for identifying cancers.
- **Generic drugs** – European antitrust regulators plan to launch another investigation into patent settlements between brand and generic pharmaceutical companies as part of a crackdown on anticompetitive deals. An official said there will probably be another monitoring exercise at the beginning of 2011, covering calendar year 2010.
- **GENZYME's Clolar (clofarabine)** + chemotherapy failed to improve overall survival (the primary endpoint) vs. chemotherapy alone in a 326-patient Phase III trial in acute myeloid leukemia. However, Clolar did double the overall remission rate to 47% (a secondary endpoint).
- **GLAXOSMITHKLINE's Avandia (rosiglitazone)** – GSK was subpoenaed by the U.S. Justice Department and received civil investigative demands from state law enforcement officials over the development and marketing of Avandia for Type 2 diabetics.
- **Gonadotropin-releasing hormone (GnRH) agonists** – The FDA added a warning to all labels in this class of prostate cancer drugs, alerting doctors and patients of the potential risk of heart disease and diabetes. These androgen deprivation drugs include: Abbott's Lupron (leuprolide depot), AstraZeneca's Zoladex (goserelin acetate),

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Bayer's Viadur (leuprolide implant), Endo Pharmaceuticals' Vantas (histrelin implant), Pfizer's Synarel (nafarelin), Sanofi-Aventis's Eligard (leuprolide acetate), and Watson Pharmaceuticals' Trelstar (triptorelin pamoate), as well as generic products.

- **LILLY** and **MACROGENICS' teplizumab** failed in a Phase III trial in Type 1 diabetes.
- **MEDICIS's Restylane** and **Perlane** – Medicis was sued by Genzyme, which claims these dermal fillers infringe its patents.
- **PFIZER** is buying a 40% interest in Brazilian generic drug-maker **Laboratorio Teuto Brasileiro** and has an option to buy the rest of the company, starting in 2014. Teuto makes both branded and unbranded generics, and Pfizer will have the right to register and sell Teuto's products in markets outside Brazil under the Pfizer name. Teuto also will be able to sell some Pfizer products under its brand in Brazil.
- **ROCHE/GENENTECH's Herceptin** was approved by the FDA to treat gastric cancer.
- **SALIX PHARMACEUTICALS** signed an agreement for the development and commercialization of **Photocure ASA**'s Lumacan, a chemical intended to make colon cancers easier to detect by turning tumor cells red when they are scanned.
- **ST. JUDE MEDICAL** is expanding its presence in the cardiovascular area with the purchase of **AGA Medical Holdings**.
- **TEVA PHARMACEUTICAL INDUSTRIES**, which has a large generic business, hired the FDA official formerly in charge of generic drugs. Gary Buehler, the deputy director of the FDA's Office of Pharmaceutical Science, and until this past March the head of the FDA's Office of Generic Drugs, will go to work for Teva on November 1, 2010. Teva dropped out of the Generic Pharmaceutical Association in June 2010, joining the newly formed Generic Drug User Fee Coalition.

NEWS IN BRIEF

AMGEN's Aranesp (darbepoetin) – safe to stay on the market

The FDA's Cardiovascular and Renal Drugs Advisory Committee voted 15-1 (with 1 abstention) that Aranesp should remain on the market for non-dialysis patients with chronic kidney disease (CKD), despite an increased risk for stroke. The panel also voted 9-5 against lowering the dose for patients with hemoglobin levels <9 g/dL. The panel recommended additional studies to find the ideal dose and to identify patients who benefit from Aranesp, and the panel voted 10-4 (with 3 abstentions) not to recommend avoiding use of Aranesp in all patients with CKD with a prior history of stroke.

AMYLIN/LILLY's Bydureon (extended-release exenatide) – delayed again by FDA

The FDA asked for additional clinical studies, particularly more information on heart rate (including a "thorough" QT prolongation study) at higher-than-therapeutic doses. The FDA also wants a study on the efficacy of the commercial formulation of Bydureon. Apparently, the FDA is worried that the drug could build up in diabetics with kidney impairment. This is the second time the FDA rejected Bydureon, and it means a significant delay for this once-weekly injectable drug for Type 2 diabetes, which uses technology from **Alkermes**. Amylin said it will do a new study and submit it by the end of 2011, which would mean that approval is unlikely before mid-2012 at the earliest.

Amyotrophic lateral sclerosis (ALS) – may be a disease of protein misfolding

A study published in ***Nature Neuroscience*** reported that an abnormal protein structure – a shape change in superoxide dismutase 1 (SOD1) protein – found in inherited cases of ALS also plays a role in sporadic cases. If these findings are confirmed, mouse models could be developed to help identify drugs (perhaps an antisense agent) that would help the majority of ALS patients. But there is also some evidence that another pathway, the TDP-43, is involved in ALS. *Is SOD1 the key or are both involved?*

BOEHRINGER INGELHEIM's Pradaxa (dabigatran etexilate) – gets FDA approval

Pradaxa was approved by the FDA for the prevention of stroke and blood clots in patients with non-valvular atrial fibrillation. Both a 75 mg BID dose and a 150 mg BID dose were approved. Why did the FDA approve a 75 mg BID dose – which the company did not request – and did not approve the 110 mg BID that the company did request? An FDA official offered this explanation:

> "In not approving the 110-mg strength, dosing options were limited for patients with severe renal insufficiency, but the Division concluded that it would be desirable to provide access to dabigatran for this patient population. Based on pharmacokinetic modeling, comparing pharmacokinetic data from RE-LY with data from a small study of subjects with compromised renal function, a dosing

regimen of 75 mg BID appears appropriate for patients with estimated CrCl (creatinine clearance) 15 to 30 mL/min. The 75-mg strength is already manufactured by (Boehringer Ingelheim) and marketed in the EU and can be marketed in the U.S. Patients with CrCl ≥31 mL/min should receive 150 mg BID."

Pradaxa is the first drug alternative to warfarin in 50 years. In announcing the approval, the FDA emphasized that Pradaxa is associated with fewer strokes than warfarin and does not require monitoring with blood tests.

BRISTOL-MYERS SQUIBB's Orencia (abatacept) – failed in lupus

In a Phase IIb trial published in ***Arthritis & Rheumatism***, Orencia missed not only the primary endpoint (new flare) but also the secondary endpoints. This was a 12-month, multi-center, double-blind, placebo-controlled, 175-patient trial in lupus patients tapered off corticosteroids. New flares occurred in 79.7% of Orencia patients and 82.5% of placebo patients, and serious adverse events were higher (19.8% vs. 6.8%). However, questions were raised about the study design that may mean the drug is not yet dead in lupus: the steroid doses were too long, the taper was prolonged, patients with active disease were excluded, patients without autoantibodies were included, the BILAG score was used, etc. A post hoc analysis – with all the problems that entails – found that BILAG A flares occurred in 40.7% of Orencia patients vs. 54.4% of placebo patients, and physician-assessed flares were 63.6% for Orencia and 82.5% for placebo.

CELLDEX THERAPEUTICS' rindopepimut (CDX-110) – effective in glioblastoma

In a study published in the ***Journal of Clinical Oncology***, this experimental vaccine targeted at epidermal growth factor receptor variant III (EGFRvIII), improved progression-free survival (PFS) and median overall survival in newly diagnosed glioblastoma patients. Duke University researchers reported that overall survival of vaccinated patients was five times better than for control.

JOHNSON & JOHNSON/MCNEIL – another Tylenol recall

J&J is recalling Tylenol 8 Hour caplets 50 count bottles at the retail level following a "small number" of complaints of a musty or moldy odor. The uncharacteristic odor is thought to be caused by the presence of trace amounts of a chemical called 2,4,6-tribromoanisole. The FDA said it considers this voluntary action to be a precaution, and all events reported so far have been temporary and non-serious. Earlier this month, bottles of Pfizer's Lipitor (atorvastatin) were recalled for a musty smell related to the bottles in which it was packaged.

Oncology drugs – insurers looking to cut costs

Several large insurance companies, including Aetna and UnitedHealthcare, have turned a spotlight on the cost of oncology drugs and experimenting with ways to lower costs, including new ways to pay oncologists. UnitedHealthcare, for example, plans a one-year project with five oncology practices in which doctors would get an additional fee if they follow standard treatments instead of "experimenting" with off-label and unproven therapies. Under this program, oncologists will receive the wholesale cost of standard drugs that they prescribe for patients and will be paid separately for their services, which will erase any economic incentives for the doctors to prescribe more-costly drugs. Oncologists will still be able to use expensive therapies, but they won't make any money on the drug itself.

Pharma research – moving away from patented drugs

A survey of 50 industry executives by Roland Berger, a strategy consultancy, found that two-thirds of large pharmas have become increasingly skeptical about the returns from future innovation and are focused on diversifying away from patented drug development:

- 65% consider their sector facing a "strategic crisis."
- 67% see diversification as a potential solution.
- Nearly 50% believe that current R&D research would yield a negative return, but two-thirds believe future scientific advances could yield positive returns over the next decade.

ROCHE/GENENTECH and BIOGEN IDEC – collaboration changes

The two companies have restricted their collaboration on anti-CD20 antibodies, specifically **ocrelizumab**, giving Genentech responsibility for further development and commercialization of ocrelizumab in multiple sclerosis (MS). Biogen Idec will receive tiered, double-digit royalties on U.S. sales of ocrelizumab that will approximate its current 30% interest in the compound. In addition, Biogen Idec will take over more responsibility (development, commercialization, and costs) for **GA-101**, a next-generation anti-CD20 antibody in development for chronic lymphoid leukemia (CLL) and non-Hodgkin's lymphoma (NHL). If GA-101 meets specific sales milestones, Biogen Idec's share of the co-promotion profits of **Rituxan** (rituximab) will decrease from 40% to 35%.

REGULATORY NEWS

FDA may get tougher on bioequivalence

A ***Bloomberg*** report quoted Dr. Janet Woodcock, director of the FDA's Center for Drug Evaluation and Research, as saying that the FDA may tighten standards for how closely generic drugs resemble brand-name equivalents in response to complaints from patients and generic drug company employees that some generic drugs do not work as well as the brand. In a speech, Dr. Woodock said, "[People] say, 'I know there are products out there that aren't equivalent,' and typically they're manufacturing folks. I've heard it enough times from enough people to believe that there are a few products that aren't meeting quality standards." *What drugs are most likely to get increased scrutiny? Perhaps digoxin, lithium, phenytoin, warfarin, and synthetic thyroid.*

FDA 510(k) reform

FDA Commissioner Dr. Margaret Hamburg told medical device manufacturers at the Advanced Medical Technology Association (AdvaMed) MedTech conference that the FDA's plan to revise the 510(k) process will be a "serious, thoughtful process" and will consider all the comments received. She also promised that there will be additional opportunities for comment, feedback, and discussion. Dr. Hamburg said the proposed changes are expected to be announced by the end of this year. However, medical device industry leaders criticized the pace of device reviews by the FDA, saying it is slowing innovation. AdvaMed CEO/president Stephen Ubl said, "Performance at the agency is deteriorating, and we believe the 510(k) process needs a tune-up, not a new engine."

Senator urges HHS to investigate high-prescribing doctors

Sen. Charles Grassley (R-IA) wrote to Health and Human Services Sec. Kathleen Sebelius demanding she investigate why some doctors prescribe huge amounts of drugs for Medicare and/or Medicaid patients. The senator's request comes after a Florida doctor was found to have written 96,685 prescriptions for mental health drugs in a 21-month period.

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
	October 2010	
October 28	**Vivus's Qnexa** (phentermine + topiramate), a diet drug	PDUFA date
	November 2010	
November 2-3	Draft of regulations for **generic biologics**	FDA public hearing
November 4-5	Public workshop on **orphan drugs**	FDA public workshop in Lansdowne VA
November 16	**GSK/Human Genome Sciences' Benlysta** (belimumab) for lupus	FDA's Arthritis Advisory Committee
November 18	**Amgen's denosumab** for cancer patients	PDUFA date
November 18	**Mela Sciences' MelaFind** for melanoma detection	FDA's General and Plastic Surgery Devices Advisory Committee
November 30	**GlaxoSmithKline/Valeant's ezogabine** for epilepsy	PDUFA date
	December 2010	
December 2	**Oceana Therapeutics' Solesta** (dextranomer in gel of stabilized non-animal hyaluronate) for fecal incontinence	FDA's Gastroenterology and Urology Devices Advisory Committee
December 3	**Allergan's Lap-Band**	FDA's Gastroenterology and Urology Devices Advisory Committee
December 7	**Orexigen Therapeutics' Contrave** (naltrexone + bupropion), a diet drug	FDA's Endocrinologic and Metabolic Drugs Advisory Committee
December 9	**GSK/Human Genome Sciences' Benlysta** (belimumab) for lupus	PDUFA date
December 16	**AstraZeneca's Brilinta** (ticagrelor), an anticoagulant	PDUFA date
December 25	**Bristol-Myers Squibb's ipilimumab** for advanced melanoma	PDUFA date
	Other future meetings	
January 7, 2011	**Endo Pharmaceuticals' tamper-resistant Opana ER** (oxymorphone), a painkiller	PDUFA date
January 31, 2011	**Orexigen Therapeutics' Contrave** (naltrexone + bupropion), a diet drug	PDUFA date
March 7, 2011	**Salix Pharmaceuticals' Xifaxan** (rifaximin) for non-constipation IBS	PDUFA date
Date TBA, 2011	Review of **accelerated drug approval process**	FDA's Oncologic Drug Products Advisory Committee (ODAC)
Summer 2011	Report on **FDA 510(k) reform**	Institute of Medicine