Trends-in-Medicine

Quick Takes

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

SHORT TAKES

- **ALLSCRIPTS/MISYS** and **ECLIPSYS** are merging.
- **BOSTON SCIENTIFIC** launched its Taxus Element drug-eluting stent in Europe.
- **CARDINAL HEALTH** will buy Healthcare Solutions for $517 million up front and possibly an additional $150 million in payments over the next three years if Healthcare Solutions reaches specified financial targets. Healthcare Solutions provides tools, services, and data to improve outcomes and increase efficiency to specialist physicians, drug companies, and managed care companies.
- **The Centers for Medicare and Medicaid Services (CMS)** has delayed until March 2011 the Joint Commission's requirement to implement telemedicine standards for both general and critical access hospitals.
- **DISCOVERY LABS' Surfaxin (lucinactant) –** The company expects to reapply for FDA approval for the drug, which is intended to treat respiratory distress in premature infants by March 2011. New preclinical tests to resolve chemistry and manufacturing problems should be completed by then. However, the company has said that it will abandon Surfaxin if the FDA requires additional clinical trials.
- **EXIQON** will discontinue the operations of its Oncotech subsidiary and liquidate the drug resistance testing company after the California Medicare Administrative Contractor, Palmetto GBA, disallowed coverage for Oncotech tests. Previously, Exiqon had hoped to sell Oncotech, but now "is exploring available options for securing an optimum financial position in light of the abandoned plans for divesting Oncotech."
- **GLAXOSMITHKLINE/HUMAN GENOME SCIENCES' Benlysta (belimumab)** has been submitted to the European Medicines Agency for the potential treatment of systemic lupus erythematosus by GSK and to the FDA by Human Genome Sciences.

- **JOHNSON & JOHNSON/CORDIS** is dropping plans to develop replacement heart valves, instead opting to pursue collaborations and partnerships with some of the emerging players already in the heart valve market. *So, is J&J shopping for a valve company to buy?*
- **MERCK's cladribine**, an oral treatment for relapsing-remitting multiple sclerosis, has been resubmitted to the FDA, following a November 2009 FDA request for more information.
- **SALIX's Xifaxan (rifaximin) –** Salix is seeking FDA approval to market Xifaxan as an irritable bowel syndrome treatment. The drug already is approved for travelers' diarrhea and hepatic encephalopathy.
- **SORIN** acquired Gish Biomedical, enhancing its extra-corporeal circulation product line. Gish makes disposable, single-use devices for cardiovascular surgery.

NEWS IN BRIEF

Allopurinol – may slow kidney disease, treat angina

Although it is used mainly to treat hyperuricemia in patients with gout, generic allopurinol may also slow the progression of chronic kidney disease (CKD) and reduce the risk of a cardiovascular event in patients with CKD, according to results of a study published in the June 10, 2010, issue of the ***Clinical Journal of the American Society of Nephrology***. Researchers assessed disease progression, cardiovascular events, and hospitalizations among 113 CKD patients randomized to receive either 100 mg allopurinol daily or standard treatment for two years. Patients receiving allopurinol showed improved kidney function, a 71% CV risk reduction, and a 62% reduction in hospitalizations vs. control. The effects were observed regardless of age, gender, proteinuria, presence of diabetes, blood levels of uric acid and C-reactive protein, and other medications used. Researchers said the results should be confirmed in a large prospective trial.

In the results of another clinical trial, reported in ***The Lancet***, 65 patients with documented coronary artery disease and stable angina were randomized to receive 600 mg allopurinol daily or placebo with standard anti-anginal therapy. Exercise tolerance tests after 6 weeks showed that 85% of patients taking allopurinol improved their time to ST depression vs. 58% of placebo patients, 78% improved exercise time vs. 45% of placebo patients.

Alzheimer's disease – pharmas sharing data

Competing drug companies, in consultation with regulators and the National Institutes of Health, have created a database including data on at least 4,000 Alzheimer's patients in an effort to share information that may help researchers develop new treatment ideas. A dozen drug companies are involved in the collaboration, and the first set of information available includes data from 11 failed Alzheimer's clinical trials conducted by Abbott, AstraZeneca, GlaxoSmithKline, Johnson & Johnson, and Sanofi-Aventis. The data will also be used to study disease progression and differences between Alzheimer's patient subgroups.

BECTON DICKINSON – sells medtech businesses

BD has agreed to sell its Ophthalmic Systems unit and the surgical blades, critical care, and extended dwell catheter product platforms of its Medical Surgical Systems unit to RoundTable Healthcare Partners for an undisclosed amount. Edward Ludwig, BD Chairman and Chief Executive Officer said, "This sale will enable BD to focus resources and management attention on opportunities which are a preferred strategic fit with the BD medical strategy, which focuses on parenteral medication delivery." The transaction is expected to be completed by the end of BD's fourth fiscal quarter 2010.

BRISTOL-MYERS SQUIBB/PFIZER's apixaban – more effective than aspirin

The AVERROES clinical trial of this experimental blood thinner in patients with atrial fibrillation who cannot tolerate standard medications such as warfarin was halted when an independent review panel determined that apixaban was more effective than aspirin for preventing stroke and embolism. The multicenter, international trial included 5,600 patients, and the companies said that apixaban demonstrated an "acceptable" safety profile compared with aspirin.

What does the AVERROES data mean for Bayer's Factor Xa inhibitor, Xarelto (rivaroxaban)? It helps establish the class of Factor Xa inhibitors, which helps both Xarelto and apixaban, but it may give apixaban a marketing advantage over Xarelto because only apixaban is likely to have an indication in warfarin-intolerant patients.

CHELSEA THERAPEUTICS' CH-4051, an oral antifolate – RA trial delayed by FDA

The FDA asked the company to delay initiation of its Phase II study of CH-4051 in rheumatoid arthritis (RA) and provide additional detail from the preliminary studies (preclinical and Phase I) previously submitted. Chelsea does not expect that the FDA request will require additional studies and is anticipating receiving written comments from the Agency in the next few weeks.

Preclinical and clinical data suggest better safety, tolerability, and potency than methotrexate (MTX), the current leading antifolate treatment and standard of care for a broad range of abnormal cell proliferation diseases. In Phase I single and multiple ascending dose studies, CH-4051 was well tolerated at doses ≤7.5 mg. The 5 mg dose was as well tolerated as placebo. High doses (10 mg and 20 mg) of CH-4051 demonstrated mostly mild toxicities, such as gastrointestinal side

effects and reversible liver enzyme elevations. No serious adverse events occurred during the studies.

The proposed 12-week Phase II trial of CH-4051 is intended to evaluate doses up to 3.0 mg daily vs. MTX 20 mg weekly in RA patients with a prior inadequate response to MTX.

The company's most advanced drug candidate, Northera (droxidopa) – an orally active synthetic precursor of norepinephrine for the treatment of neurogenic orthostatic hypotension – has begun a pivotal Phase III trial (Study 306).

DAIICHI SANKYO's Benicar (olmesartan) – FDA starts safety review

The FDA is conducting an ongoing safety review of this angiotensin receptor blocker and will evaluate data from two clinical trials showing a higher cardiovascular death rate in patients taking the drug. The FDA said it has not concluded that Benicar increases the risk of death and currently believes that the benefits of Benicar in patients with high blood pressure continue to outweigh the potential risks. The two trials involved are ORIENT and ROADMAP, in which Type 2 diabetics were randomized to receive Benicar or placebo to determine if Benicar slowed the progression of kidney disease. There were a greater number of deaths due to heart attack, stroke, or sudden death among patients taking Benicar.

DEPOMED's DM-1796 (gabapentin extended release) – NDA filed for postherpetic neuralgia

A new drug application for once-daily oral administration of DM-1796 to manage pain due to postherpetic neuralgia was accepted by the FDA. The extended release formula is intended to reduce dosing frequency and side effects. The NDA was based on the results of a randomized, placebo-controlled, Phase III trial showing that DM-1796 patients had a significantly reduced average daily pain score vs. placebo patients.

Diclofenac – riskiest NSAID

Data from a Danish registry of more than 1 million healthy, non-steroidal anti-inflammatory drug (NSAID) users between 1997 and 2005 revealed that diclofenac is associated with a 91% increase in risk for fatal heart attack or stroke. The risk increased with increasing dosages, researchers reported in ***Circulation: Cardiovascular Quality and Outcomes***. The risk associated with diclofenac was greater – a 66% increased risk – than that seen with Merck's Vioxx (rofecoxib), which was withdrawn from the market. The study also showed a 29% increase in risk of fatal or non-fatal stroke with ibuprofen use and no increased risk with naproxen use.

Electronic medical records (EMRs) – challenges to clinical use of data

A study, conducted by HIMSS Analytics, a wholly owned, not-for-profit subsidiary of the Healthcare Information and Management Systems Society (HIMSS), and sponsored by Anvita Health, looked at the challenges in use of EMR data and found that:

- Payors and providers underestimate how clinical analytics can improve the quality of patient care and reduce costs.
- Key obstacle to better use of clinical data –
  - For payors is integration – a common language that ties together multiple data formats.
  - For providers is (a) missing data and (b) capturing data in compatible formats from multiple places.
- Payors want real-time analytics. Currently, most clinical data are analyzed retrospectively, with little use of data for real-time decision making. Meaningful use guidelines should begin to address this.
- Payors and providers both want evidence-based solutions.
- Both providers and payors recognize that government incentives will drive the need for more sophisticated clinical analytics. Payors, in particular, expect that the next-generation clinical analytics will generate information that will drive high quality, cost-effective care.

Five personal genomics companies – told their tests need FDA 510(k) approval

The FDA sent regulatory letters to five genomics companies – 23andMe, Navigenics, deCODE, Knome, and Illumina – advising them that the FDA believes they are manufacturing and selling direct-to-consumer (DTC) products (diagnostic devices) without appropriate FDA clearance or approval.

These are not "Warning Letters" but "Untitled Letters," an important distinction. Warning Letters set out specific violations of law that a company must address immediately or face FDA enforcement action, but Untitled Letters identify FDA concerns and give a company the opportunity to meet with the Agency and take steps to address those concerns. If a company doesn't respond properly to an Untitled Letter, it could then get a Warning Letter.

Daniel Vorhaus, an attorney at Robinson Bradshaw & Hinson and editor of the firm's ***Genomics Law Report***, said the implications of this "aggressive regulatory action" are several-fold, including:

- The FDA has categorized the tests as "devices."
- The FDA appears to have decided that these tests are "clinical interpretations" that will be used in healthcare decisions.
- The FDA refers variously to "patient" and "consumer" use.

- The FDA appears concerned with off-label use of approved tests.
- The FDA does not consider the tests "laboratory-developed tests (LDTs)," which the Agency historically has chosen not to regulate.
- It is not clear whether the FDA considers these tests Class I, Class II, or Class III devices.
- The FDA has not set a timeframe for the companies to respond except to ask them to do so promptly.
- The FDA left the door open for some tests to be exempt from review.

What does this FDA action mean for these five companies, specifically? Vorhaus said, "The immediate implications of the FDA's letters may be less significant than some might initially suspect. After years of speculation about whether and how the FDA would regulate DTC genetic testing products, the Agency has now publicly delivered at least a partial answer: It considers ***these specific products*** to be medical devices requiring either premarket clearance or approval, and it does not consider them to be LDTs subject to regulatory enforcement discretion. For the companies named in the letters …this provides a concrete Agency determination to which they can react. It's unlikely that the response from any of the companies will be to pull their products completely off of the market."

What are the options for these five companies? Vorhaus suggested:

- Pull the product from the market.
- Seek FDA approval.
- Alter the product so it no longer requires premarket approval or clearance.
- Challenge the FDA.

What does all this mean for the broader genetic testing industry? Vorhaus said, "For the rest of the industry, the regulatory outlook is little clearer today than it was yesterday. The FDA has offered specific regulatory determinations for a limited set of DTC genetic testing products, but it has not offered broader industry guidance…It is clear enough that the Agency considered several important factors in identifying these five specific companies and products as regulatory targets. These include the DTC availability of the product (or …contribution to DTC availability), the perceived medical use of the product, and…the complexity of the testing and interpretation involved in the product. But how the FDA weighed those factors against others – including the utility of the tests, the reality of its limited regulatory resources, and the presence of numerous other genetic tests offered to consumers and to patients – remains unclear…There continues to be a lack of clarity into the FDA's DTC genetic testing regulatory strategy …My own opinion continues to be that transparency – and not regulation – is what would be most beneficial to the DTC genetic testing industry and its customers at this time. Until companies, consumers and regulators better understand the tests that are available and, importantly, how those tests are being used, it will be difficult to develop a regulatory policy that protects the health and safety of individuals without stifling commercial innovation and individual exploration. In the meantime, expect the FDA's latest actions – as well as, possibly, the ongoing congressional investigation – to significantly shake up the personal genomics landscape in the coming weeks and months."

IMMUNOMEDICS' TF2 – preclinical colon cancer studies positive

Pretargeted therapy with TF2, an antibody specific against both carcinoembryonic antigen and a small peptide, delayed tumor growth and prolonged survival in animals with CEA-expressing human colonic tumors. The pretargeted radiation therapy extended median survival from 13 days in untreated animals to 65 days in one study, and from 25 days to 48 days in another. Bone marrow and kidney toxicity was temporary and mild, and weight loss was minimal. Based on these preclinical results, TF2 is currently being tested in two Phase I clinical trials in patients with colorectal cancer.

LANTHEUS's flurpiridaz F18 injection – promising cardiac imaging results

Cardiac perfusion imaging using PET with this investigational F18 agent produced significantly better images and rendered a significantly larger perfusion defect size compared with SPECT imaging. Researchers at Cedars-Sinai Medical Center in Los Angeles conducted a study with 26 patients who underwent both F18 PET and SPECT within a 6-month period. Image quality with the F18 PET was excellent in 24 patients and good in 2. With SPECT, image quality was excellent in 17, good in 8, and fair in 1.

In a separate study reported at the Society of Nuclear Medicine annual meeting, flurpiridaz F18 PET with molecular imaging was conducted in 6 patients in a Phase II trial. Researchers were able to generate motion-free cardiac perfusion images by combining amplitude-based respiratory gating and motion frozen processing. Researchers said the technique is feasible and provides significantly improved image resolution, contrast, and contrast-to-noise.

MANNKIND's Afrezza (inhaled insulin, also known as Technosphere) – non-inferior to standard therapy

Inhaled Afrezza works as well as standard therapy with Lilly's injectable Humalog (insulin lispro), according to results of a trial reported by MannKind. The 16-week study included 130 patients with Type 1 diabetes inadequately controlled with other treatments. Patients were randomized to receive Afrezza or Humalog with glargine or basal insulin. MannKind reported

that Afrezza was "clearly non-inferior" to Humalog in terms of reducing HbA_{1c} levels in patients with Type 1 diabetes and was associated with significantly lower rates of hypoglycemic episodes; lower post-prandial glucose levels at 30, 60, 90, and 120 days; and lower fasting blood glucose levels.

MERCK's MK-4305, a dual orexin receptor antagonist – in Phase III sleep trials

MK-4305 is in Phase III trials in insomnia, with younger patients receiving 40 mg or 20 mg doses and elderly patients receiving 30 mg or 15 mg doses. A Phase IIb trial in 254 patients with primary insomnia showed that 4 weeks of MK-4305 was significantly more effective than placebo for improving overall sleep efficiency. Merck expects to seek FDA approval for the drug in 2012.

NOVO NORDISK's Victoza (liraglutide) – cardiovascular outcomes trial announced

The cardiovascular safety of this once-daily human GLP-1 analog in Type 2 diabetics will be assessed in a long-term, international Phase IIIb trial. The randomized, double-blind, placebo-controlled trial will enroll 9,000 patients with Type 2 diabetes and will compare cardiovascular outcomes among those treated with Victoza and standard diabetes treatments vs. those treated with standard therapy alone for up to 5 years.

PHARMASSET's RG-7128 – successful Phase II study in HCV

The company reported that this oral investigational hepatitis C treatment met key Phase II trial goals. In a 408-patient, 12-week study, 80% of RG-7128 patients had undetectable HCV RNA levels vs. 50% of patients receiving standard therapy (interferon + ribavirin). In addition, RG-7128 met safety and tolerability goals.

REGENERON's Arcalyst (rilonacept) – showed promise in gout trial

Regeneron reported that patients taking Arcalyst in one clinical trial experienced an 80% reduction in recurrent gout flares. However, a second trial showed that the drug didn't reduce pain due to gout once a flare occurred. Regeneron expects to seek FDA approval for Arcalyst in 2011 if additional clinical trials are successful.

Repetitive Transcranial Magnetic Stimulation (rTMS) – use approved in refractory depression

The University of Alabama at Birmingham received FDA approval to use its rTMS technology for treating depression in patients who have failed standard antidepressant therapy. rTMS delivers MRI-strength magnetic pulses to specific parts of the brain during daily sessions for several weeks. The magnetic pulses usually induce sustained activation of the targeted area within 4-6 weeks, alleviating depressive symptoms in more than half of patients. One-third of patients in clinical trials experienced complete remission of their depression.

ROCHE/GENENTECH's Avastin (bevacizumab)

- **kidney function monitoring suggested in cancer patients –** The results of a study published in the ***Journal of the American Society of Nephrology*** showed that Avastin may be associated with severe proteinuria that can lead to significant kidney damage and compromise the efficacy of cancer treatment with the drug. Researchers said that the results suggest physicians should monitor kidney function in patients taking this angiogenesis inhibitor.

- **better for AMD –** Avastin was superior to Roche/Genentech's Lucentis (ranibizumab) in a study of 131 patients with wet age-related macular degeneration (AMD). The study results were reported in the ***British Medical Journal***.

Rotavirus vaccines – new contraindication

The Centers for Disease Control and Prevention (CDC) issued new guidance adding severe combined immunodeficiency (SCID) to the list of contraindications to receiving the vaccine. The guidance, which applies to both GlaxoSmithKline's Rotarix and Merck's RotaTeq, was announced in the June 11 issue of ***Morbidity and Mortality Weekly Report***. There were eight cases of vaccine-acquired rotavirus infection in infants with SCID since the approval of RotaTeq in 2006.

ST. JUDE MEDICAL – settles whistleblower False Claims Act suit

St. Jude Medical will pay $3.7 million to settle a False Claims Act charge by the U.S. Department of Justice, but the company admitted no wrongdoing. The suit alleged that St. Jude paid kickbacks to Parma Community General Hospital in Ohio and Norton Healthcare in Kentucky in an effort to secure business for its heart devices. St. Jude said, "The allegations centered on small, isolated product rebates paid more than five years ago."

VITAL THERAPIES' Extracorporeal Liver Assist Device (ELAD) system – trial expanded to Europe

Two patients have been enrolled in the European expansion of the SILVER trial, which will assess this biological cellular therapy's ability to prevent deterioration of liver function and improve survival in patients with acute chronic liver failure. SILVER is an open-label, randomized, 80-patient, 20-center, international trial. So far, 29 patients have been enrolled at 11 U.S. centers and one London center.

FDA NEWS

Upcoming FDA Advisory Committees of Interest

Date	Topic	Committee
June 24	"Identifying Unmet Public Health Needs and Facilitating Innovation in Medical Device Development"	CDRH public hearing
July 13-14	**GlaxoSmithKline's Avandia** (rosiglitazone) cardiovascular safety – and to a lesser extent the safety of **Takeda's Actos** (pioglitazone)	Joint meeting of the Endocrinologic and Metabolic Drugs Advisory Committee ***and*** the Drug Safety and Risk Management Advisory Committee
July 15	**Vivus's diet drug Qnexa** (phentermine + topiramate)	Endocrinologic and Metabolic Drugs Advisory Committee
July 20	**Roche/Genentech's Avastin** (bevacizumab) – two supplemental BLAs for naïve metastatic HER2-negative breast cancer	Oncologic Drugs Advisory Committee (ODAC)
July 22-23	**REMS for long-acting opioids**	Joint meeting of the Anesthetic and Life Support Drugs Advisory Committee ***and*** the Drug Safety and Risk Management Advisory Committee
July 28	**AstraZeneca's Brilinta** (ticagrelor)	Cardiovascular and Renal Drugs Advisory Committee
September 17 (not confirmed)	**Boehringer Ingelheim's Pradaxa** (dabigatran)	Cardiovascular and Renal Drugs Advisory Committee