Trends-in-Medicine

Quick Takes

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Trends-in-Medicine
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June 20, 2010

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

SHORT TAKES

- **ABBOTT** will pay $575 million for exclusive global rights to **Neurocrine Biosciences' elagolix**, which is in Phase II trials for treatment of uterine fibroids and pain caused by endometriosis.
- **ATRICURE's AtriClip**, a left atrial appendage exclusion system for preventing blood clots during cardiac procedures, has been cleared (approved) by the FDA. The company plans to launch the device in 2010.
- **AUXILIUM's Xiaflex (collagenase clostridium histolyticum) –** The company received a warning letter from the FDA about marketing claims. The FDA found a patient brochure for Xiaflex misleadingly suggested that the injectable treatment for Dupuytren's disease can be used to treat ***all*** patients with the disease, including those with early disease, but Xiaflex is only approved to treat contracture with a palpable cord.
- **Biodegradable coronary stents –** A ***CRTonline.org*** survey found that 45% of cardiologists believe biodegradable stents will be a niche product, while 30% predicted they will become the workhorse stent, 18% said they will only be used for patients who cannot take Sanofi-Aventis's Plavix (clopidogrel), and 6% do not expect them to have a role at all in coronary arteries.
- **CANNABIS SCIENCE**, a pharmaceutical cannabis developer, will acquire Montana Pain Management, a for-profit clinic that has successfully negotiated with the Montana Department of Health and Human Services to allow medical marijuana reimbursement through the state Medicaid spend-down program.
- **COVIDIEN** will pay $250 million to acquire all shares of Somanetics, which are valued at $300 million. Covidien already distributes the Somanetics' In-Vivo Optical Spectroscopy Cerebral/Somatic Oximeter in Europe, the Middle East, and Africa.

- **GENZYME's Campath (alemtuzumab)** has received fast-track designation from the FDA for the treatment of relapsing-remitting multiple sclerosis. It is already approved to treat chronic lymphocytic leukemia (CLL).
- **GLAXOSMITHKLINE's MenHibrix vaccine –** The FDA has asked for more information before approving this dual vaccine, intended to protect against both meningococcal disease and haemophilus influenzae type b.
- **HALT MEDICAL's 2000GI –** The FDA cleared the company's electrosurgical system for treatment of tumors through soft tissue ablation with radiofrequency (RF) energy.
- **HEALTHTRONICS' Cryocare CS system**, a kidney and prostate cancer treatment which uses extreme cold delivered to tumors, received FDA clearance.
- **IMMUNOMEDICS' milatuzumab (an anti-CD-74 monoclonal antibody conjugated with doxorubicin) –** The first patient with relapsed multiple myeloma has been dosed in a Phase I/II safety trial that will test four doses.
- **Japan –** ***Sankei Shimbun***, a Japanese newspaper, reported that Japan will allow the use of drugs and devices approved outside of the country but not approved in Japan yet. The government will choose 200 Japanese medical institutions by 2020 that will be permitted to use treatments that haven't received Japanese approval.
- **MERCK's Gardasil (HPV vaccine) –** The FDA has extended its review of an application to extend Gardasil use to older women. The company now expects a response from the FDA by the end of 2010.
- **OREXIGEN's Contrave (naltrexone SR/bupropion SR) –** The PDUFA date for this anti-obesity drug is January 31, 2011.
- **PHYTOPHARM's Cogane (PYM-50028) –** Phase II trials using this neurotrophic factor inducer in Parkinson's disease have been given the go-ahead by the FDA.
- **SANBIO's SB-623 –** The FDA has approved a clinical trial using the company's bioengineered derivative of human bone marrow stromal cells for treatment of disability caused by stroke.
- **SANOFI-AVENTIS's Jevtana (cabazitaxel)** received FDA approval under the priority review program for treatment of advanced, hormone-refractory prostate cancer that worsens despite prior treatment with docetaxel. Median survival among 755 patients was 15.1 months for Jevtana-treated patients vs. 12.7 months for patients on mitoxantrone chemotherapy.

NEWS IN BRIEF

ACCME – new rule prohibits CME industry presentations at medical conferences

The Accreditation Council for Continuing Medical Education (ACCME) issued a new rule prohibiting pharmaceutical company researchers and scientists from presenting during meetings offering continuing medical education (CME) credit to physician attendees, and it is causing quite a stir. The rule, which is intended to remove drug industry influence and conflict of interest from medical educational activities, was discussed during a National Institutes of Health (NIH) meeting during which American Heart Association (AHA) president Dr. Clyde Yancy said his organization would aggressively appeal the ACCME decision. The AHA annual meeting, one of the largest medical meetings in the world, will be held in November 2010 in Chicago. Although the policy would only eliminate about 100 of the 3,000 abstracts scheduled to be presented during AHA, the organization receives an estimated $1.7 million from pharmaceutical and device manufacturers for CME activities annually.

The rule also affects all other meetings, including the Endocrine Society annual meeting, which began Saturday, June 17, 2010. Endocrine Society president Dr. Robert Vigersky issued a statement saying that his society will no longer offer CME credit for any oral abstract or poster presentation sessions at its meetings. If more organizations follow such a strategy, it would be a hardship for many physicians who depend on attendance at their specialty society's annual meeting to amass state-required CME credits. Another solution would be to allow industry employees to give only non-CME presentations.

Attendees at the NIH meeting mostly agreed that the rule goes too far. However, some researchers and medical educators believe that the rule is a good policy.

ADOLOR/PFIZER's ADL-5859/ADL-5747 – both delta agonists failed in pain trial

The results of a Phase II trial in 400 patients with pain caused by knee osteoarthritis showed that neither agent was better than placebo or oxycodone. Adolor said that patients in the trial experienced a strong pain reduction with placebo, which may have contributed to the failure of the investigational drugs. In the study, patients were randomized to receive 150 mg of ADL-5859, 150 mg of ADL-5747, 20 mg of oxycodone, or placebo. Adolor will decide with partner Pfizer whether to pursue development of the agents for treatment of chronic inflammatory pain. A trial of ADL-5747 for post-herpetic neuralgia pain is ongoing, with results expected in 1Q11.

AMYLIN's Bydureon (exenatide for extended-release injectable suspension) – beat Januvia but not metformin or Actos

This long-acting injectable diabetes medication was superior to Merck's Januvia (sitagliptin) but no more effective than other agents, including generic metformin, in an 820-patient clinical trial. Amylin said Bydureon reduced blood glucose levels by 1.5% vs. 1.2% with Januvia and 1.5% with metformin and 1.6% with Takeda's Actos (pioglitazone). The PDUFA date is October 22, 2010, and the ***San Diego Union Tribune*** reported that the company will ***not*** submit results from this study to the FDA.

BAYER/ONYX's Nexavar (sorafenib) – fails to increase survival in NSCLC

In a trial of 900 patients with non-squamous, non-small cell lung cancer (NSCLC), the combination of Nexavar and chemotherapy did not extend survival, although patients did not experience a worsening of their disease. Despite these results, the companies will continue to investigate Nexavar in lung cancer. The drug is also being used in trials for cancers of the thyroid, breast, ovaries, and colon.

BIOTRONIK – launched MRI-safer pacemaker and leads

The MRI-compatible Evia pacemaker and Safio leads were launched in Europe. Medtronic paved the way for MRI-compatible cardiac devices with European approval in June 2009 of its Advisa SureScan pacemaker, and an FDA advisory committee recommended approval of Advisa SureScan, but the FDA has not yet made a decision. *Watch for other companies to follow suit with their own MRI-compatible devices.*

Computer-aided breast cancer detection – reimbursement trumps efficacy evidence

Healthcare providers have been quick to adopt digital breast cancer screening despite a lack of evidence that it has any benefit over conventional screening mammography. Use of the advanced technology ballooned from <5% of patients in 2001 to >25% in 2003, possibly due to Congress mandating Medicare coverage for the digital test, which increased reimbursement from $86 to $106, researchers hypothesized in the June 14, 2010, issue of ***Archives of Internal Medicine***.

The authors pooled data from small studies showing that computer-aided detection may be better than traditional mammography for detecting breast cancers and determined that an additional 50 cancers would be detected for every 100,000 women undergoing the digital screening. However, the digital screening would result in more than 1,000 false positive tests, causing an estimated 80 women to undergo unnecessary biopsies. The researchers added that many women receiving false positive results would also suffer anxiety or depression for no reason.

CURIS' GDC-0449 – misses colon cancer trial goal

This hedgehog pathway inhibitor, which is being developed as a colon cancer treatment, failed to increase survival in a 199-patient Phase II colon cancer trial which compared GDC-0449 + Genentech's Avastin (bevacizumab) to standard treatment. Researchers found no difference in survival between the two regimens. This was the largest trial using GDC-0449 to date.

DURECT's Posidur (bupivacaine) – meets 1 of 2 study goals

In a Phase IIb European trial of 115 women requiring therapy for post-surgical pain, Posidur was as effective as a commercially available injectable anesthetic and placebo for reducing pain intensity during the first three postop days. However, patient use of rescue opioid pain medications during that period was ***not*** reduced with Posidur treatment. Durect said that a U.S. Phase III trial is currently enrolling patients and that partner Nycomed is continuing European enrollment of patients in a Posidur trial for pain after shoulder surgery.

ESPERION – teams with Cleveland Clinic to develop HDL drugs

Esperion, which developed the blockbuster statin sold by Pfizer – Lipitor (atorvastatin) – has entered a research agreement with the Cleveland Clinic to find ways to develop treatments that will raise high-density lipoprotein (HDL) levels. The Cleveland Clinic previously worked with an Esperion founder to develop and test a genetic treatment intended to raise HDL, but it proved too difficult and costly to develop.

HEARTWARE's HVAD – to start destination therapy trial

The company received conditional approval from the FDA to begin enrollment in an Investigational Device Exemption (IDE) trial, ENDURANCE, of this left ventricular assist device (LVAD) as ***destination therapy***. ENDURANCE is a randomized, unblinded, multicenter, non-inferiority study of ≤450 patients vs. Thoratec's HeartMate-II. The primary end-point is stroke-free survival at two years. Meanwhile, ~11 implants have been performed so far in the bridge-to-transplant study, with the relatively slow enrollment possibly due to the time required for IRB approvals.

HRA's ellaOne (ulipristal acetate) – FDA panel recommends approval

The FDA's Reproductive Health Drugs advisory committee voted 11 to 0 to recommend approval of the emergency birth control pill. Available in Europe, ellaOne is effective for preventing pregnancy when taken within five days of unprotected intercourse or contraceptive failure.

HUMAN GENOME SCIENCE'S Zalbin/Joulferon (albinterferon alfa-2b) – approval unlikely for biweekly dose

The company received a discipline review letter from the FDA indicating the Agency has concerns about the 900 µg biweekly dosing used in the application submitted for Zalbin, a potential hepatitis C virus (HCV) treatment. Although the FDA is still reviewing the application, the company said the feedback suggests it is unlikely that the biweekly Zalbin dose will be approved. In April 2010 Human Genome's European partner, Novartis, withdrew the European marketing application for Joulferon outside the U.S., after regulators indicated they might request additional information before approval. In March 2010, positive data from a clinical trial testing a monthly dose of Zalbin were reported, and Human Genome and Novartis are considering developing the treatment with the less frequent dosing regimen.

JOHNSON & JOHNSON/DEPUY ORTHOPEDICS – first ASR lawsuit filed

A lawsuit alleging that the company delayed informing consumers that its metal-on-metal ASR hip replacement was likely to fail, resulting in a delayed diagnosis and repeat hip replacement in one patient, was filed in U.S. Federal District Court in Ft. Myers FL. The case was filed by a consortium of law firms representing patients throughout the country interested in pursuing claims against J&J. DePuy halted sales of the ASR earlier this year, but only after a ***New York Times*** article detailed the high early failure rate being reported with the device was published in March 2010.

Medicare – to revise coverage of anemia drugs for kidney patients

The Centers for Medicare and Medicaid Services (CMS) is opening a National Coverage Decision on erythropoiesis-stimulating agents (ESAs) – Amgen's Epogen (epoetin alfa) and Aranesp (darbepoetin alfa) and Johnson & Johnson's Procrit (epoetin alfa, manufactured by Amgen) – for the treatment of anemia in chronic kidney disease (CKD) patients based on cardiovascular safety concerns.

In 2007, CMS issued an NCD on ESA use in cancer-related anemia but had not done so for either dialysis patients or pre-dialysis patients, though some local carriers have policies in effect. However, CMS will phase in "bundling" payments to dialysis centers for medications (including ESAs) and services into one lump sum starting in January 2011. The new payment system will be fully implemented by 2014.

The NCD for CKD does not come as a surprise. CMS was expected to adjust its coverage/reimbursement to be closer in line with the FDA labeling for ESAs. There has been a strong feeling that the drugs are overused and even improperly used in the U.S. As of last year ~235,000 of the 350,000 dialysis patients and ~81,000 of the nearly 20 million non-dialysis chronic kidney disease patients in the U.S. were taking an ESA.

In March 2010, CMS's Medicare Evidence Development and Coverage Advisory Committee (MEDCAC) met to consider the safety of ESAs in anemia related to CKD. At the time, Dr. Barry Straube, director and chief clinical officer in CMS's Office of Clinical Standards and Quality, said he had not decided whether to open an NCD, but CMS "felt the need to be proactive and start drilling down and analyzing what the current evidence is [about the safety of these drugs]."

The MEDCAC agreed that there is sufficient evidence to make a determination that ESAs affect health outcomes in CKD patients, finding that:

- Maintaining or raising hemoglobin <12 g/dL with ESAs ***improves*** exercise toleration, survival, and quality of life, but ***not*** vascular events.
- Maintaining/raising hemoglobin >12 g/dL with ESAs ***worsens*** vascular events and survival.
- More data are needed on hyporesponders and pediatric patients.
- Hemoglobin may not be a good surrogate marker.

Dr. Louis Jacques, director of CMS's Coverage and Analysis Group, told the panel at the end of the meeting, "The sense I've gotten is that Hb <9 is good, >12 is bad, and from 10-12 is uncertain."

Amgen is hoping that CMS will set a hemoglobin range of 10-12 g/dL for all chronic kidney disease patients, which is the current FDA labeling.

CMS is accepting comments until July 16, 2010, with a decision expected by March 2011. The FDA's Cardiovascular and Renal Products Advisory Committee is expected to meet later this year to discuss ESA use and safety.

MERCK's Stimuvax (BLP-25 liposome vaccine) – FDA gives okay to continue trials

The FDA released a hold on 2 of 3 Phase III trials using this cancer treatment, so both a global lung cancer trial and a trial in Asian patients with lung cancer will go forward. The third trial, designed to test the vaccine in patients with breast cancer, is still delayed, and Merck said it continues to discuss the trial with the FDA. The FDA halted the Stimuvax trials in March 2010 after a case of encephalitis developed among 30 patients in a Phase II trial of Stimuvax + cyclophosphamide.

NMT MEDICAL's StarFlex – PFO closure for stroke no better than medical therapy

Preliminary results of the CLOSURE-1 StarFlex trial of patent foramen ovale (PFO) closure showed that the device was no

better than standard medical treatment for preventing recurrent stroke and transient ischemic attacks (TIAs). NMT said that closure rates in the trial were similar to those seen in other trials, 87%, and that adverse events were low. Although there was a small trend toward a benefit for StarFlex PFO closure, the difference was not significant. *The questions are (1) whether cardiologists will stop doing PFO closure for stroke based on this trial, and (2) what the impact will be on other companies with stroke PFO closure trials underway, including AGA Medical.*

NOVARTIS's BHQ-880 – promising for bone regeneration

This experimental, bone regeneration, monoclonal antibody showed promise in regenerating bone in 11 of 34 patients with multiple myeloma. Researchers hope that the novel treatment will improve bone density, reduce bone pain, and reduce fractures caused by the disease. In the trial, patients responded to a combination of BHQ-880 and Novartis's Zometa (zoledronic acid), with a ≤6% increase in bone density. No significant adverse reactions were observed. Researchers noted BHQ-880 does not have any effect on the cancer.

NOVO NORDISK – resuming diabetes drug sales in Greece

Novo Nordisk will resume selling its diabetes drugs in Greece now that health officials there have increased drug prices. In May 2010, Greece cut the price it pays for drugs by 25% because of its economic crisis. Novo Nordisk said Greek prices are still 7%-8% lower than an average of the three lowest national European prices.

OXFORD BIOMEDICA's ProSavin – delivery modified

The FDA has approved a modified delivery of this genetic therapy for Parkinson's disease in order to reduce surgical time and allow for an increased dose. The therapy is delivered by injection directly to the brain. In a Phase I/II safety trial in three patients, two patients had a sustained 30% improvement of Parkinson's disease symptoms for two years after treatment. In addition, patients either experienced stabilization or a reduced need for L-DOPA therapy.

PFIZER/WYETH's Rapamune (rapamycin) – Congress investigating

The House Oversight and Government Reform Committee is investigating whether the company illegally promoted Rapamune for unapproved uses. Rapamune is approved to prevent organ rejection following kidney transplantation. The committee aims to determine "whether Wyeth aggressively encouraged the use of Rapamune to prevent organ rejection following heart, lung, liver, pancreas, and islet cell transplants, without FDA approval." Pfizer has until June 28, 2010, to respond to the allegations.

REPROS' Proellex (telapristone) – FDA allows new clinical trial

After nearly a 1-year delay because there were concerns about the hepatic effects of Proellex, the FDA has agreed to allow Repros to conduct a new clinical trial with the agent, which is intended to reduce menstrual bleeding associated with uterine fibroids and endometriosis. The 12-woman trial will use lower doses of Proellex to determine safety and will test Proellex doses ranging from 1 mg to 12 mg for 10 weeks vs. placebo. The company said that weekly liver function tests will be performed throughout the trial and that patients will be independently monitored to detect any safety concerns.

ROCHE's taspoglutide – delayed due to hypersensitivity

The FDA review of this potential diabetes drug has been delayed by 12-18 months while Roche puts together a risk mitigation and evaluation strategy (REMS) to apply to additional clinical trials. There were hypersensitivity reactions to taspoglutide, including gastrointestinal symptoms and skin reactions, in a greater number of patients than would normally be expected. Roche hopes to be able to identify patients who are more likely to experience hypersensitivity reactions before proceeding with the drug. Roche had initially expected to ask the FDA to review taspoglutide in 2011; no new action date has been announced yet.

Stem cell therapy – new complication reported

A report in the ***Journal of the American Society of Nephrology*** notes a previously unreported complication in a patient receiving injections of her own stem cells for treatment of kidney cancer. After a few months of treatment, the patient developed bleeding in the treated kidney, requiring removal of the organ. The affected kidney also developed angiomyeloproliferative masses, which the researchers believe were caused by the stem cell administration. An accompanying editorial pointed out that the patient was being treated in a private clinic, and the stem cell therapy may not have been overseen by the scientific community.

FDA NEWS

FDA and NIH collaborate on personalized medicine

FDA and the National Institutes of Health (NIH) are coordinating initiatives designed to facilitate the development and availability of gene-based therapies, according to an article in the ***New England Journal of Medicine***. The initiatives will support the advancement of personalized medicine through rapid development, review, and approval. NIH will invest in research on translating genetic marker discoveries into effective diagnostic tests and treatments, while the FDA will develop a timely pathway for the review and approval of the resulting therapies. The initiatives also aim to ensure that developed genetic therapies are administered effectively.

Safety summaries to be posted on FDA website

In an effort to provide patients and healthcare professionals with drug and biologic safety information earlier, the FDA will post summaries of safety analyses on recently approved products on the FDA website. The initial reports posted will include information on products approved since September 2007. Brief discussions of any steps the FDA is taking to address any identified safety concerns will also be included in the summaries. Dr. Robert Ball, director of the Office of Biostatistics and Epidemiology in the Center for Biologics Evaluation and Research (CBER), said, "These summaries will provide clear and useful information in a timely manner that can be used by providers and patients to make informed decisions about an individual's health."

Stricter outsourcing regulations on horizon

FDA officials said they will propose stricter regulations aiming to ensure the purity and safety of drugs manufactured by outsourced entities. The FDA is considering a requirement that pharmas conduct their own audits of outsourced manufacturing facilities and wants to make sponsoring companies more accountable for verifying that outside manufacturing contractors follow FDA regulations. Currently, drug companies can review data from outsourced manufacturers without conducting on-site inspections.

Study on uptake of new drugs/devices

A recent analysis of FDA advisory panel activity by Concept Capital's Washington Research Group found:

- 70% of all applications for new therapies or new uses for approved products received positive advisory committee recommendations between 2007 and 2010.
- The rate of recommendations for approval varied from a low of 55% (12 of 22 drugs) for the Oncologic Drugs Advisory Committee (ODAC) to 100% for the Peripheral and Central Nervous System Drug Advisory Committee.
- In addition, they reported that the Endocrinologic and Metabolic Drugs Advisory Committee recommended approval for 7 of 8 drugs it reviewed during the past four years.

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Upcoming FDA Advisory Committees of Interest *(items in red are new since last week)*

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 19-20	**Oversight of laboratory-developed tests**, especially genetic tests	Public meeting
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 27-28	Meeting to obtain input on issues and challenges associated with the development and implementation of risk evaluation and mitigation strategies (**REMS**)	Public hearing
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