TRENDS-in-MEDICINE

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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…

Trends-in-Medicine
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SHORT TAKES

- **AMGEN and MICROMET** – The two companies signed a cancer drug development deal which focuses on Micromet's antibodies, called BiTE, which are designed to direct T-cells to attack tumor cells. Sanofi, Boehringer Ingelheim, and Bayer Schering Pharma also have collaboration agreements with Micromet.
- **ANTARES PHARMA's Anturol (transdermal oxybutynin ATD gel)** – **Watson Pharmaceuticals** licensed this potential treatment for overactive bladder from Antares. The FDA PDUFA date is December 8, 2011.
- **BAXTER and HALOZYME THERAPEUTICS' HyQ** – This injectable combination of Halozyme's drug absorption enzyme rHuPH20 and Baxter's immune globulin product made from donated blood had positive results in a Phase III trial of 89 patients with a lifelong immunodeficiency condition. The patients had an average 0.025 serious bacterial infections per year vs. the minimum one infection per year set for the trial. The companies submitted HyQ to the FDA, and the PDUFA date is April 30, 2012.
- **Cancer studies** – A study published in the ***Journal of Clinical Oncology*** found that a "substantial" number of Phase III trials of systemic cancer treatments with potential influence on clinical practice remain unpublished after ≥6.5 years.
- **CELGENE's Actimid (pomalidomide)** – The Medical College of Georgia is conducting a Phase I trial on this thalidomide derivative to treat sickle cell disease.
- **ELLIPSE TECHNOLOGIES' MAGEC** – The company said that preliminary clinical data suggest that children with early onset scoliosis can be treated safely and effectively with this remote-controlled, non-invasive MAGnetic Expansion Control (MAGEC) treatment.
- **Giant salvinia** – Researchers at the National Center for Pharmaceutical Crops at Stephen F. Austin State University and MD Anderson Cancer Center are studying this invasive water weed to see if it can treat cancer, saying that the plant in its purest form can shrink human tumor cells without being very toxic to normal cells.
- **GILEAD's Truvada (tenofovir + emtricitabine)** – Eleven new analyses of the iPrEx study confirmed the long-term efficacy and safety of pre-exposure prophylaxis (PrEP) with Truvada to prevent HIV infection. The analyses will be presented at the International AIDS Society (IAS) Conference on HIV Pathogenesis, Treatment, and Prevention in Rome which just started.
- **HUMAN GENOME SCIENCES and GLAXOSMITHKLINE's Benlysta (belimumab)** – Health Canada approved this lupus drug, which received FDA approval in March 2011.

- **INVIVO THERAPEUTICS' biopolymer scaffold** – The company asked the FDA for an investigational device exemption (IDE) for an open-label study in 10 spine patients. The device, which provides support during the acute stage of a spinal cord injury, is customized by a neurosurgeon to fit a spinal cord lesion, ingrained into a patient's spinal cord, and then biodegrades over 12 weeks.

- **NEWRON PHARMACEUTICALS' NW-3509** – The company asked the FDA to allow it to begin clinical trials of this new schizophrenia drug, which targets voltage-gated sodium channels in order to normalize aberrant neuronal firing and glutamatergic hyperactivity, which have been implicated in the pathophysiology of schizophrenia.

- **NOVARTIS' Lucentis (ranibizumab)** – The U.K.'s National Institute for Health and Clinical Excellence (NICE) preliminarily rejected this drug for patients with diabetic macular edema (DME), saying that it wasn't cost-effective. A final decision is expected in August 2011.

- **NSAIDs** – Older patients with hypertension and coronary artery disease who use non-steroidal anti-inflammatory drugs (NSAIDs) chronically for pain are at a significantly increased risk for cardiovascular events, according to research published in ***The American Journal of Medicine***. Long-term NSAID users had a 47% increase in the rate of death as well as non-fatal heart attack vs. intermittent NSAID users. After five years, those rates increased to 126% for death and 66% for heart attack.

- **OHR PHARMACEUTICAL's Evizon (squalamine)** – The company said two animal studies of its eye drops for wet-age related macular degeneration (AMD) found that Evizon is safe and enters the tissues in the back of the eye in concentrations known to block choroidal neovascularization.

- **PFIZER's Lipitor (atorvastatin)** – The European Union extended the patent for this cholesterol-lowering drug by six months, until May 2012, in exchange for availability of a chewable version for patients age ≥10.

- **PHARMATHENE's SparVax** – The company said that this experimental anthrax vaccine showed stability for ≤3 years.

- **Primary ovarian insufficiency (POI)** – Researchers at the University of California, San Francisco, (UCSF) and the National Institutes of Health (NIH) are developing a test to predict a woman's risk of developing this menopause-like condition, which affects women decades before they would normally develop symptoms of actual menopause.

- **ST. JUDE MEDICAL's Libra** – The FDA is allowing the company to expand a trial of this deep brain stimulation system in patients with major depressive disorder from three to 20 sites with a total of 125 patients.

- **SEATTLE GENETICS and TAKEDA's Adcetris (brentuximab vedotin)** – The FDA's Oncologic Drugs Advisory Committee (ODAC) unanimously recommended that this chemotherapy drug be approved for patients with Hodgkin's lymphoma who have already had a stem cell transplant and for patients with relapsed/refractory systemic anaplastic large-cell lymphoma.

- **SHIRE's Vyvanse (lisdexamfetamine)** – This hyperactivity drug may limit overeating by interacting with chemicals in the brain that affect mood, motivation, and inhibition. The company plans to try to get FDA clearance through the psychiatric approval route rather than as a diet drug, since several diet drugs have been rejected by the Agency's Metabolism and Endocrinology Products Division because of side effects.

- **Therapeutic hypothermia** – Despite negative studies in the past, a new study suggests this approach to treating sudden cardiac arrest patients with hypothermia is beneficial. In a study published in ***Circulation***, 92% of 140 out-of-hospital cardiac arrest patients who had this treatment and were discharged had positive neurological outcomes, with most or all of their cognitive function intact.

- **Toxoplasmosis** – Researchers at the Massachusetts Institute of Technology (MIT) discovered that *Toxoplasma gondii,* a protein in a strain of a common parasite, can suppress inflammation in an infected host. The parasite *Toxoplasma* infects about a third of the world's population and more than 60 million people in the U.S. carry the parasite.

- **TRANSCEPT PHARMACEUTICALS' Intermezzo (zolpidem tartate sublingual)** – In another setback, the company received a complete response letter from the FDA for this insomnia drug due to continued safety concerns. The drug has faced regulatory delay since 2009.

- **VALEANT** is buying **Dermik**, Sanofi's dermatology unit. Dermik's portfolio includes acne treatment BenzaClin (benzoyl peroxide/clindamycin topical), keratosis treatment Carac (fluorouracil), and the dermal filler Sculptra (poly-L-lactic acid). Valeant also is buying the ortho dermatologics divison of Janssen Pharmaceuticals, a **Johnson & Johnson** company.

- **VICAL and ASTELLAS PHARMA's TransVax** – The two companies plan to collaborate on this cytomegalovirus vaccine designed to prevent a potentially fatal virus in stem cell transplant patients. They expect to start a multinational Phase III trial in 1H12.

- **ZOGENIX' Relday (risperidone)** – The company, by teaming with **Durect**, has created an extended-release formulation of Johnson & Johnson's antipsychotic, Risperdal (risperidone), that is oral and once-monthly. Human trials are expected to start in early 2012.

NEWS IN BRIEF

Amiodarone – generic as safe as the brand

A study published in the ***Canadian Medical Association Journal*** found that atrial fibrillation patients taking the generic version of this antiarrhythmic had no higher risk of thyroid problems than patients taking branded amiodarone. The researchers reported that the total incidence rate for thyroid dysfunction was 14.1 per 100 person-years for both brand and generic amiodarone. The mean time to clinical thyroid dysfunction was 4.32 years with the brand and 4.09 years with a generic.

Emphysema – telomere length linked to risk

Telomeres, the body's cellular clocks, may be a critical factor underlying the development of emphysema, according to a study published in the ***American Journal of Respiratory and Critical Care Medicine***. Researchers said that mice with short telomeres had a significantly increased risk of developing emphysema after exposure to cigarette smoke for six hours a day, five days a week for six months. Telomeres are DNA protein structures that protect chromosome ends from degrading. Their length is genetically determined, but they also shorten progressively with cell division. Short telomeres are considered a marker of aging in cells. Principal investigator Mary Armanios, MD, of Johns Hopkins said, "These results are one of the clearest examples of telomere length, which is an inherited factor, interacting with an environmental insult to cause disease. In fact, our results in mice suggest that short telomeres might contribute to how cigarette smoke accelerates aging in the lung in some individuals."

Indirubin – may block brain tumors

This active ingredient from a traditional Chinese herbal remedy blocks human glioblastoma invasion in mice, according to a study published in ***Cancer Research***. Ohio State University researchers said that indirubin "successfully blocked human glioblastoma cells from invading mouse brains or moving once they are inside them," suggesting this could become the basis for a treatment for this deadly brain tumor. Indirubin is derived from the indigo plant and is the active ingredient in a Chinese remedy for chronic myeloid leukemia (CML).

MEDTRONIC

- **Simplicity** – The FDA gave conditional approval to start enrolling patients for a trial of this catheter system, which delivers low-power radiofrequency (RF) energy to renal arteries in order to treat high blood pressure.
- **SynchroMed II** – Medtronic issued an urgent device correction for a small percentage of these implantable pain drug pumps after receiving reports of faulty batteries that could cause the devices to malfunction. The company said that the pumps will not be recalled and should not be removed unless the devices show reduced battery performance.

REGENERON PHARMACEUTICALS and SANOFI's sarilumab – reduces RA symptoms

A Phase II trial showed that sarilumab + methotrexate reduced symptoms of moderate-to-severe rheumatoid arthritis (RA) in more patients than patients on methotrexate alone. Symptoms improved by ≥20% for 49% of patients taking the lowest of five doses and for 72% of patients in the highest-dose group vs. 46.2% of methotrexate only patients.

ROCHE

- **BACE1 antibody** – Roche researchers have developed an antibody that crosses the blood-brain barrier more efficiently, according to two papers published in ***Science Translational Medicine***. In the first study, researchers tested an antibody to the beta-secretase 1 (BACE1) protein, which plays a role in amyloid production associated with Alzheimer's disease, and found that while it was effective at blocking BACE1 function in test tubes, it was only modestly successful in reducing the function of BACE1 in the brain, even when given at high doses. In the second study, a re-engineered antibody enriched in the mouse brain and led to a greater reduction of amyloid-beta in the brain after a single systemic dose.
- **Omnitarg (pertuzumab)** – A Phase III trial found that combining Omnitarg with Herceptin and docetaxel in women with HER2-positive metastatic breast cancer extended progression-free survival (PFS) longer than just Herceptin/docetaxel, and no new safety signals were observed. Adverse events were consistent with those seen in previous studies.
- **Tamiflu (oseltamivir)** – The company this month is removing the 12 mg/mL oral suspension and replacing it with a new dose of 6 mg/mL in order to avoid measuring mistakes due to frothiness.

SANOFI

- **Multaq (dronedarone)** – The European Medicines Agency (EMA) broadened its safety review of this anticoagulant for atrial fibrillation after the Phase III PALLAS trial for expanded use was halted because of a higher incidence of cardiovascular problems. EMA experts will decide what to do at a July 18-21, 2011, meeting.
- **Lemtrada (alemtuzumab)** – In a Phase III trial of 581 patients with early stage multiple sclerosis, the drug met one primary endpoint, showing a significant reduction in annual relapses. However, Lemtrada missed a second primary endpoint, failing to significantly reduce progression of disability vs. Merck Serono's Rebif (interferon beta-1a).

Parkinson's disease – controversy over the cause

Lewy bodies have been the hallmark of Parkinson's disease pathology for many years, but a controversial hypothesis about where and how Parkinson's disease starts is getting more attention. The new theory is that it begins in the intestinal nervous system as a reaction to some pathogen, perhaps from a virus that enters the body through the nose – not in the substantia negra – and moves along the vagus nerve upward toward the brain, progressing in predictable stages to the brainstem, the midbrain, and finally to higher brain regions, not reaching the substantia negra until Stage 3. *Watch for this controversy to generate new approaches to drug development for Parkinson's disease.*

TITAN PHARMACEUTICALS' Probuphine (buprenorphine) – superior to placebo

Phase III study results of an implantable formulation of this opioid addiction drug showed that more patients stayed "clean" over six months vs. sham implant and that the device was non-inferior to Reckitt Benckiser's Suboxone (naloxone and buprenorphine), the standard sublingual formulation. Titan said that it will release the percentages on mean urine negatives from the three arms of the trial later this year.

Transvaginal surgical mesh – FDA warning and hearing

The FDA warned doctors that the surgical placement of mesh to repair pelvic organ prolapse (POP) may expose patients to greater risk compared to other options and does not carry greater clinical benefit. The FDA warned that the mesh can erode through vaginal tissue causing pain, infection, bleeding, pain during intercourse, and urinary problems. The Agency also warned that there is a risk of organ perforation during the surgical procedure to install the mesh.

In 2010, there were at least 100,000 POP repairs that used surgical mesh, and ~75,000 of these were transvaginal procedures. William Maisel, MD, deputy director and chief scientist at the FDA's Center for Devices and Radiologic Health, said, "There are clear risks associated with the transvaginal replacement of mesh to treat POP…Mesh is a permanent implant. Complete removal may not be possible and may not result in complete resolution of complications." The FDA plans to take the issue to a two-day meeting of the Obstetrics and Gynecology Devices Advisory Committee on September 8-9, 2011.

REGULATORY NEWS

China stepping up complaint handling

China plans to set up a telephone network over the next five years to respond to public complaints about its food and drug sector, detect illegal food and drug producers, and crack down on illegal activities. *This is a very small step in the right direction.*

FDA relaxing restrictions for testing new Alzheimer's drugs

The FDA will allow some patients with swelling or bleeding in the brain to stay in certain trials.

FDA guidelines for targeted treatments

The FDA is asking for public comment on proposed guidelines that will require targeted treatments and companion diagnostic tests to undergo simultaneous reviews. The Agency said that it might approve a targeted drug without approving a companion test if the treatment is designed to treat a life-threatening disease or if there are labeling changes to already approved drugs.

FDA needs more oversight of imports

The Pew Health Group said that the FDA "needs much more power to protect the U.S. supply of drugs as more and more are made in other countries."

FDA makes senior staff changes

After a review of how the Office of the Commissioner is structured, FDA Commissioner Margaret Hamburg, MD, decided to make some changes aimed at addressing the

challenges of scope, innovation, administration, and globalization. These changes, which will actually shrink the size of the immediate office of the Commissioner, include:

- A new chain of command, with "directorates" reporting to the Commissioner. Among the new directorates will be:
  - Global Regulatory Operations and Policy. Deborah Autor, now Director of CDER's Office of Compliance will become Deputy Commissioner of this office.
  - A directorate focused on global food and drug production/supply.
  - The already established Office of Foods.
  - The Office of Operations, to be headed by a chief operating officer (COO), who will oversee the Agency's administrative functions (human resources, information technology, etc.). A search has begun to find someone for this job.
- A new office of Deputy Commissioner for Medical Products and Tobacco to provide high-level coordination and leadership across the Centers for drug, biologics, medical devices, and tobacco products. However, those Centers will continue to operate as discrete management entities under their current leadership. The new official, Steven Spielberg, MD – former Dean of Dartmouth Medical School and currently Director of the Center for Personalized Medicine and Therapeutic Innovation at Children's Mercy Hospital in Kansas City – will also oversee the FDA's Special Medical programs.

In addition, the FDA announced these new positions:

- Heidi Marchand, PharmD, as the new assistant commissioner, Office of Special Health Issues (OSHI), Office of External Affairs in the Office of the Commissioner.
- Elizabeth Dickinson, associate chief counsel for drugs, will be acting chief counsel starting August 7, replacing current chief counsel, Ralph Tyler, who is leaving August 5, 2011.

HHS to issue medical device identifiers

The Department of Health and Human Services (HHS) notified the FDA that in September 2012 it plans to publish a proposed rule establishing unique identifiers for medical devices. Under the rule, the identifier will identify a device through distribution and use and may include the lot or serial number.

U.K.'s NICE to continue to influence decisions

NICE expects to continue to play a central role in drug pricing and usage in the U.K. even after the new national drug pricing system goes into effect. ***Reuters*** reported that NICE head Andrew Dillon said that he envisages "evolutionary" change as the current system is replaced in January 2014 with a new system that rewards manufacturers with higher prices for the most effective, innovative, and needed new medicines.

FDA approvals/clearances

- **4SC's resminostat** – orphan drug status for this hepatocellular carcinoma (HCC) drug, which is in Phase II trials. The trial is also being tested in patients with Hodgkin's lymphoma and colorectal cancer in KRAS-mutant patients.
- **ACTIVIEWS' CT-Guide** – a needle guidance system, which works with a miniature video camera which fastens to medical tools, received 510(k) approval.
- **COOK MEDICAL's Zenith Spiral-Z** – an abdominal aortic aneurysm (AAA) iliac leg graft.
- **ST. JUDE MEDICAL's Epiducer** – a lead delivery system which works with the company's Eon neurostimulator device to treat chronic pain in the trunk and limbs of the body stemming from failed back surgery.
- **TEARSCIENCE's LipiFlow** – a system which detects and treats evaporative dry eye by warming oil glands in patients' eyelids received 510(k) clearance.

European approvals

- **BRISTOL-MYERS SQUIBB's Yervoy (ipilimumab)** – for adults with previously treated advanced melanoma.
- **HUMAN GENOME SCIENCES and GLAXOSMITHKLINE's Benlysta (belimumab)** – for lupus patients resistant to standard therapies.
- **ST. JUDE MEDICAL's Ilumien** – a diagnostic system to help detect and treat coronary artery disease with a wireless tool called Wi-Box, which enables the receipt of aortic pressure readings and other data.

FDA recalls

Each month the FDA issues a report on its recalls, which sometimes contain items that were not announced earlier. Major recalls are often listed in Short Takes or News in Brief, but this also may be of some interest to ***Quick Takes*** readers:

- **BIOMET's Oxford knee** – 12 implants recalled in Europe due to a customer complaint that while peeling off the Tyvek lid on the blister pack, very little effort was required to remove it, which could lead to contamination of the device.
- **COVIDIEN's Uri-Drain** – urinary control devices due to contamination.

- **ENDO PHARMACEUTICALS/AMS' AMS 800 and AMS Acticon Neosphincter Control Pumps –** all unexpired units due to the possibility of malfunctions.
- **GE HEALTHCARE's Infusable and InfusaScan Pressure Infusors –** due to leaks that may affect pressure. Nearly a million units are involved.
- **SAFECOR HEALTH –** numerous products for lack of FDA approval.
- **STAAR SURGICAL's nanoFlex IOL –** due to an error in the directions for use.
- **TEVA's lansoprazole –** due to color deviations.
- **VARIAN MEDICAL SYSTEMS' Eclipse Radiation Treatment Planning System –** due to possible dose delivery errors of ≤10%.

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 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 20	**Unnamed gastroenterology drug:** Closed discussion and review	Joint meeting of the FDA's Gastrointestinal Drug Advisory Committee and the Drug Safety and Risk Management Advisory Committee
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 Adcetris** (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
September 7	Design of clinical trials for systemic antibacterial agents for the **treatment of acute otitis media**	FDA public workshop
September 8	**Johnson & Johnson's Xarelto** (rivaroxaban) for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation	FDA's Cardiovascular and Renal Drugs Advisory Committee
September 8-9	Safety of **transvaginal mesh** for pelvic organ prolapse	FDA's Obstetrics and Gynecology Devices Advisory Committee
September 9	Safety of **bisphosphonates** in osteoporosis	Joint meeting of the FDA's Reproductive Health Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee
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** (transdermal oxybutynin ATD 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*)
April 30	**Baxter and Halozyme's HyQ** for immunodeficiency	PDUFA date