TRENDS-in-MEDICINE

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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…

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SHORT TAKES

- **ACHILLION PHARMACEUTICALS' sovaprevir (ACH-1625) –** The company said a 39-patient Phase II trial of this investigational hepatitis C drug had favorable interim results when given in conjunction with pegylated interferon + ribavirin.

- **AENOVA GROUP**, which produces drugs for a variety of pharmaceutical and healthcare industries, was sold by **Bridgepoint** to **BC Partners**.

- **AGENNIX's talactoferrin –** The company said this investigational treatment for refractory non-small cell lung cancer (NSCLC) missed the primary endpoint in a 742-patient Phase III trial, failing to show a benefit in terms of overall survival. Talactoferrin also failed to show a benefit on progression-free survival (PFS). As a result, the company is stopping another U.S. trial of the drug.

- **AMERISOURCEBERGEN –** The Department of Justice and the Drug Enforcement Administration subpoenaed documents from the company about how it keeps controlled substances (e.g., opioids) away from inappropriate users. The subpoena was part of a grand jury investigation into prescription painkiller abuse.

- **ASTRAZENECA and BTG's CytoFab (AZD-9773) –** A Phase IIb trial in severe sepsis failed, with no significant improvement in ventilator-free days or mortality. The companies are suspending further development, and AstraZeneca is giving the drug back to BTG.

- **Breast cancer –** Research published in ***Cancer Research***, a journal of the American Association for Cancer Research (AACR), found that the protein transient receptor potential melastatin-like 7 (TRPM7) is a critical determinant of breast cancer cell metastasis. The researchers reported that reducing TRPM7 expression in invasive human breast cancer cells impaired their ability to migrate *in vitro* and impaired their metastatic potential when transferred into mice. *Watch for someone to develop an anti-TRPM7 drug.*

- **CARDIODX's Corus CAD gene expression test –** The company said a major Medicare contractor has agreed to cover the cost of this cardiac test retroactive to January 1, 2012.

- **CELSION's ThermoDox (thermally-sensitive liposomal doxorubicin) –** The FDA gave the company permission to start an ~52-patient Phase II trial of this drug in conjunction with **Royal Philips Electronics' Sonalleve** MR-guided high-intensity focused ultrasound device to treat bone metastases.

- **CURVEBEAM's pedCat, a weight-bearing CT foot and ankle scanning device** – While this device has FDA 510(k) approval, reimbursement has been a problem – and that has slowed sales – because the Centers for Medicare and Medicaid Services (CMS) covers it only when performed by a medical doctor, and the healthcare professionals most interested in it are podiatrists.

- **CYTOMEDIX's AutoloGel** – CMS agreed to cover this autologous platelet-rich plasma (PRP) gel for patients with chronic diabetic and pressure wounds – but only for patients in approved clinical trials. AutoloGel was approved by the FDA in 2007 as a medical device.

- **ECHO THERAPEUTICS' Symphony** – The company reported that a 15-patient Phase II study of this needle-free, transdermal continuous glucose monitoring device for critical care patients undergoing major general surgery and cardiothoracic surgery was positive. A Phase III trial is planned.

- **Flu vaccine** – In an article published in the journal ***Science***, researchers from Scripps Research Institute and Crucell Vaccine Institute reported that they have discovered a human antibody that protects against essentially all influenza A and B strains. The discovery could lead to a universal flu vaccine, effective against nearly all flu strains, that could be delivered in a one-time shot.

- **JOHNSON & JOHNSON's** marketing practices are under scrutiny by the Department of Justice (DOJ), which is looking at marketing of the antibiotic **Doribax** (doripenem for injection) and **Acclarent's Relieva Stratus MicroFlow Spacer** medical device.

- **KV PHARMACEUTICAL** filed for Chapter 11 bankruptcy, blaming the FDA and Medicaid for preventing it from attaining the "full value of its **Makena** (hydroxyprogesterone caproate), a drug to prevent premature birth, by not limiting compounding.

- **LUNDBECK's AE-58054** – The company reportedly is in talks with several potential partners to help develop this drug, which targets 5-HT6 receptors in the brain, as a treatment for Alzheimer's disease.

- **LUPIN's Suprax (cefixime)** – The Centers for Disease Control and Prevention (CDC) withdrew its recommendation for use of this antibiotic to treat gonorrhea because of signs of bacterial resistance. This leaves just generic injectable ceftriaxone as the only option.

- **Myotonic dystrophy** – In an article in the journal ***Neuron***, researchers from the University of Florida reported on their identification of a gene responsible for brain-related symptoms – memory loss, learning difficulties, and extreme daytime sleepiness – in the most common form of adult-onset muscular dystrophy, myotonic dystrophy.

- **NOVARTIS**, in conjunction with the University of Pennsylvania, is funding a $20 million research center – the Center for Advanced Cellular Therapies – that is expected to open next year. The deal gives Novartis technology that uses manipulated immune-system cells to fight cancer. Last year, University of Pennsylvania researchers reported positive results in several patients with advanced chronic lymphocytic leukemia (CLL) who were treated using the new technique, including two complete remissions.

- **PHILOSYS' Gmate Smart** – a blood glucose monitor that can be used with an iPad, iPhone, or iPod – was submitted to the FDA for approval. The company is hoping for approval in 3Q12.

- **RECKITT BENCKISER's Subutex (buprenorphine) and ALKERMES/ELAN's ReVia and Vivitrol (naltrexone)** – A rat study by researchers at the National Institute on Drug Abuse suggests that combining these two drugs may work to treat cocaine addiction and perhaps even methamphetamine addiction as well as heroin and opioid addiction. A human trial is being planned.

- **SALIX PHARMACEUTICALS' Xifaxan (rifaximin)** – The company licensed an extended-release formulation of this antibiotic from **Alfa Wassermann S.p.A.** Salix will have exclusive rights in the U.S. and Canada for gastrointestinal and respiratory indications, including Crohn's disease.

- **TEVA** is being investigated by the Securities and Exchange Commission (SEC) over whether it violated a U.S. law that prohibits bribery of foreign officials – in this case Latin American officials. Teva received a subpoena for documents in connection with its business practices in Latin America.

- **VIROPHARMA's Cinryze (C1 esterase inhibitor)** – After turning the company down earlier this year, the FDA has now given ViroPharma permission to expand its manufacturing of this hereditary angioedema (HAE) treatment.

NEWS IN BRIEF

AMGEN

- **Epogen (epoetin alfa).** An analysis of Medicare data found that hospitals and clinics are being overpaid for this anemia drug. Reimbursement is based on EPO usage in 2007 for dialysis, but current usage is ≥25% less. Therefore, CMS said it plans to reassess current payment rates.

Amgen also said it plans to idle production at its only bulk Epogen plant because Epogen loses patent protection in 2013.

- **Ganitumab (AMG-479).** The company, along with Japanese partner **Takeda**, said it is stopping a Phase III trial of this insulin growth factor-1 treatment for metastatic pancreatic cancer after an analysis by the independent data monitoring committee found that adding it to **Lilly's Gemzar** (gemcitabine) probably wouldn't improve survival any more than Gemzar alone. A separate Phase II trial also is being stopped.

ASTRAZENECA's Crestor (rosuvastatin) – more benefits than risks

A new study by Brigham and Women's Hospital researchers of the ~18,000-patient JUPITER trial of Crestor, published in ***The Lancet***, found that the 28% increased risk of diabetes with this statin (and all statins in general) is outweighed by a 39% decrease in the risk of a heart attack, stroke, or cardiac death. In other words, 134 cardiovascular complications or deaths were avoided for every 54 new cases of diabetes diagnosed over two years. The researchers discovered that most of the excess diabetes cases occurred in certain statin users who had already been on the verge of getting the disease due to obesity, elevated glucose levels, or insulin resistance.

Diabetes – possible vaccine cure for Type 1 diabetes

The bacillus Calmette-Guérin (BCG) vaccine, an old vaccine for tuberculosis, might be able to delay or prevent Type 1 diabetes. In a six-patient study published in the journal ***PLoS ONE***, the vaccine stimulated production of tumor necrosis factor (TNF), which killed the T cells that attack pancreatic beta cells and increased the level of regulatory T cells, with signs of new – though temporary – insulin production. While high doses of TNF can be toxic, the TNF levels generated by the vaccine appear to be not only safe but also beneficial.

JOHNSON & JOHNSON, PFIZER, and ELAN'S bapineuzumab – IV formulation fails again

Intravenous bapineuzumab, an anti-beta amyloid antibody, missed both co-primary endpoints (change in cognitive and functional performance vs. placebo) in Study 301, a second Phase III trial in mild-to-moderate Alzheimer's disease patients, this time patients without the ApoE4 genotype. In Study 302, it failed in patients with the ApoE4 genotype.

J&J and Pfizer announced that they are discontinuing all other IV bapineuzumab studies, including extension studies. There were no new safety concerns, with pneumonia, brain edema, syncope, and convulsion the most common adverse events.

However, J&J said it is not discontinuing development of bapineuzumab entirely. A Phase II neuroimaging study of subcutaneous bapineuzumab is continuing. And the companies left the door open for further studies in earlier-stage Alzheimer's or mild cognitive impairment.

Data from Study 302 as well as Study 301 will be presented as late-breakers at the European Federation of Neurological Societies (EFNS) meeting in Stockholm in September 2012.

MERCK

- **Tredaptive (niacin + laropiprant) + simvastatin.** Merck put development of this cholesterol-lowering combination on indefinite hold due to "business reasons" related to an ongoing "pipeline review."
- **Vytorin (ezetimibe + simvastatin).** The company announced that the results of the 18,000-patient IMPROVE-IT outcomes trial comparing this cholesterol-lowering combination to simvastatin alone will not be released until 2014, a year later than expected.

Percutaneous aortic valves – LBBB conveys mortality risk

A 679-patient Dutch study published in ***Circulation: Journal of the American Heart Association*** found that patients who develop left bundle-branch block (LBBB) post transcatheter aortic valve implantation (TAVI) are at an increased risk of death. Thirty-four percent of the patients developed LBBB after TAVI, and their 1-year all-cause mortality was significantly higher than TAVI patients who did not get LBBB (26.6% vs. 17.5%, p=0.006). This translated to an absolute mortality risk increase of 9.1% and a relative mortality risk of 52% for LBBB patients.

The risk of developing LBBB was significantly greater with Medtronic's CoreValve than with Edwards Lifesciences' Sapien (51.1% vs. 12%). The researchers commented, "[LBBB] appears to depend on the device being used," adding that LBBB should not be considered a harmless side effect.

ROCHE/GENENTECH's Avastin (bevacizumab)

- **Positive glioblastoma results.** Roche announced that Avastin – combined with radiation and chemotherapy with **Merck's Temodar** (temozolomide) – met a co-primary endpoint, significantly increasing PFS in glioblastoma

patients in the randomized, double-blind, placebo-controlled Phase III AVAglio trial. The complete results – including the other co-primary endpoint (overall survival) – are expected in 2013.

- **Negative results in renal cell carcinoma (RCC).** Adding Avastin to **Pfizer's Torisel** (temsirolimus) did not improve progression-free survival more than standard therapy with Avastin + interferon-alfa-2a in the Phase III INTORACT trial in advanced RCC.

ROCHE/GENENTECH's Herceptin (trastuzumab) – subq non-inferior to IV

A randomized, 24-month, 596-patient, Phase III study published in ***The Lancet Oncology*** found that a subcutaneous formulation of Herceptin in neoadjuvant breast cancer met both primary endpoints (pathologic complete response and serum trough concentration), showing non-inferiority to intravenous Herceptin with better convenience (a 600 mg injection once every three weeks).

Phase III Results with Subcutaneous Herceptin		
Measurement	**Subcutaneous Herceptin**	**Intravenous Herceptin**
Primary endpoint #1: Mean serum trough concentration	69.0 µg/mL	51.8 µg/mL
Primary endpoint #2: Pathologic complete response	45.4%	40.7%
Grade 3-5 adverse events		
Neutropenia	~30%	
Febrile neutropenia	~4%-5%	
Serious adverse events	21%*	12%

* More infections

ST. JUDE MEDICAL's Riata and Riata ST – lead failures associated with worse survival

A study published in ***HeartRhythm*** found that these cardiac leads have higher electrical failure rates long term vs. other leads. The researchers reported the five-year survival rate for Riata/Riata ST was 97.5% vs. 99.2% with **Medtronic's Sprint Quattro Secure** and 99.5% for **Boston Scientific's Endotak Reliance G/SG** leads (both $p<0.0001$). In comparison, the five-year survival with **Medtronic's Sprint Fidelis** lead, which was recalled for lead fractures, was 89.6%.

STRYKER's Wingspan – remains on market, but use restricted

The FDA rejected a petition by Public Citizen's Health Research Group to ban this brain stent, but the FDA narrowed the indications for use of the stent, which is approved under a humanitarian device exemption (HDE) to open clogged arteries in the brain. The FDA is now saying that the devices should be used only for a small segment of patients: those who have experienced multiple strokes but have not had any stroke symptoms in the previous seven days. The FDA said data on use of the devices over the past seven years suggested that some Wingspan patients may have a ***greater*** risk of stroke and death than those receiving only medical management.

Jeffrey Shuren, MD, director of the FDA's Center for Devices and Radiological Health (CDRH), said, "The FDA believes this device should remain available for this specific subgroup of patients who have exhausted other options." However, Sidney Wolfe, MD, director of Public Citizen's Health Research Group, said the FDA ignored evidence from a National Institutes of Health-funded study (SAMMPRIS) that found that for every 11 patients treated with Wingspan, one additional patient dies or has a stroke within 30 days, adding, "This is further evidence that the Agency is not making decisions in an evidence-based manner but, rather, stating that it believes the device will be beneficial, despite evidence to the contrary."

REGULATORY NEWS

Legislation to close clinical trial loopholes

A bill (HR 6272), the Trial and Experimental Studies Transparency Act of 2012, was introduced in the House of Representatives by Rep. Edward Markey (D-MA), Rosa DeLauro (D-CT), Janice Schakowsky (D-IL), and Henry Waxman (D-CA) that would require that results from ***all*** eligible clinical studies be posted on **ClinicalTrials.gov** within one year of the trial's completion, including trials conducted outside the U.S. in support of FDA applications. In addition, all interventional biomedical trials on humans would have to be registered in the database before enrolling participants. Results for studies on therapies that have never been approved for any use would have to be posted within two years of trial completion.

FDA should be more specific about nanotechnology regulations

The FDA's Pharmaceutical Science and Clinical Pharmacology Advisory Committee told the Agency that its regulation of nanotechnology in medical products whether to deliver more active ingredient or as an excipient – needs to be beefed up and be more specific. One area of particular concern to the panel was how to regulate sunscreens that contain nanoparticles. One panel member commented, "It seems as if we have more questions than answers yet we continue to see a proliferation of this…We're not even sure how to measure nanoparticles."

Among the recommendations from panel members were:

- Focus on problematic administration route (e.g., creams and sprays).
- Ask drug regulators from other countries for help, especially in characterizing nanomaterials.
- Only allow manufacturers to use nanoparticles when it is absolutely necessary.

FDA approvals/clearances

- **ABBOTT's Omnilink Elite** stent was approved for use in peripheral vascular interventions in patients with atherosclerotic iliac artery lesions.
- **ACTUATED MEDICAL's TubeClear**, a device used to remove blockages in feeding tubes without disconnecting them from patients, was cleared for use.
- **BAUSCH + LOMB and TECHNOLAS PERFECT VISION's Victus Femtosecond Laser Platform** was cleared for use.
- **GANEDEN BIOTECH's GanedenBC30** – The FDA gave this probiotic Generally Recognized As Safe (GRAS) status, which will allow its use in baked goods, beverages, and other food items.
- **GENO's GeNOsyl MV-1000** system, which provides continuous delivery of inhaled nitric oxide, was approved.
- **JOHNSON & JOHNSON**
  - **Depuy Synthes' MedStream Programmable Infusion System**, which uses a catheter to administer baclofen into the spinal canal to treat spasticity, was granted premarket application (PMA) approval.
  - **Ethicon Endo-Surgery's Harmonic ACE+ Shears**, an ultrasonic surgical device, received 510(k) clearance.
- **NEUROMETRIX's Sensus**, a pain management device to treat diabetic neuropathy, received 510(k) clearance.
- **PERRIGO's morphine sulfate oral solution** was approved to treat moderate-to-severe chronic or acute pain.
- **ROCHE/GENENTECH's Lucentis (ranibizumab)** was approved to treat diabetic macular edema (DME).
- **SUNSHINE HEART's C-Pulse Heart Assist System**, an implantable cardiac assist device, was granted ***conditional*** approval, which will allow the company to provide this new version of the device to patients enrolled in its North American feasibility trial in patients with mid-stage heart failure.
- **TALON THERAPEUTICS' Marqibo (vincristine sulfate liposome injection)** received accelerated approval to treat refractory Philadelphia chromosome negative (Ph-) acute lymphoblastic leukemia (ALL), but there is a boxed warning that it must be administered only intravenously because it is deadly if administered any other way, such as into the spinal fluid. The boxed warning also says that Marqibo has different dosage recommendations than vincristine sulfate injection alone, and to avoid overdose, doctors need to verify the drug name and dose before administration.
- **TOSHIBA AMERICA MEDICAL SYSTEMS and NEOCOIL's** 16-element, flexible coil device, designed for use with **Toshiba's Vantage Titan** 1.5-tesla MRI scanner, was cleared for use.

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FDA recalls/warnings

- **JOHNSON & JOHNSON/ETHICON ENDO-SURGERY's Proximate surgical staplers** – More than 500 lots were pulled from the market over performance issues that could make the devices misfire.
- **QUANTA AESTHETIC LASERS USA's Quanta System Q-Plus T** – The FDA sent the company a warning letter that this Q-switch Nd:YAG laser (532 nm and 1064 nm) – which is approved to treat vascular lesions, pigmented lesions, for hair and tattoo removal, and for incision, excision, ablation, and vaporization of soft tissue for general dermatology – was being improperly promoted for skin rejuvenation, skin lifting, skin tightening/smoothness, acne treatments, anti-aging, firming, and treatment of scars and keloids. In addition, the FDA said the addition of 1320 nm, 755 nm, 2940 nm, radiofrequency, and intense light-pulsed hand pieces was done without FDA approval.

European regulatory actions

- **CURVEBEAM's pedCAT** – The company applied for a CE Mark for this 3D imaging ankle and foot scanner.
- **GLAXOSMITHKLINE's Votrient (pazopanib)** received expanded approval from the European Commission to treat patients with advanced soft tissue sarcoma who already received chemotherapy or whose disease advanced within a year after neoadjuvant treatment.
- **PLURISTEM THERAPEUTICS' PLacental eXpanded (PLX) cells** – The Paul-Ehrlich-Institut, Germany's medical regulator, authorized a Phase I/II trial of this therapy in 18 patients undergoing total hip replacement.

U.K.'s National Institute for Health and Clinical Excellence (NICE) news

ROCHE's Zelboraf (vemurafenib) – NICE asked for more information about the cost of this melanoma treatment before it will decide whether to recommend use in the National Health Service (NHS). When NICE rejected Zelboraf in June 2012, Roche cut the price, but NICE still doesn't appear satisfied.

Regulatory news from other countries

China: **COVIDIEN** opened a research & development center in Shanghai and plans to hire >300 people over the next 3 years.

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
	August 2012	
August 17	**Amarin's Vascepa** (icosapent ethyl, AMR-101), an FDA-approved omega-3 fatty acid for lowering high triglycerides	FDA decision expected on NCE status
August 21	**Pfizer's tofacitinib**, an oral JAK2 inhibitor for rheumatoid arthritis	PDUFA date (but this probably will be delayed)
August 27	**Gilead Sciences' Quad** (emtricitabine+tenofovir+elvitegravir+cobicistat) for HIV	PDUFA date
August 28	**Discussion of reporting requirements** for Division of Cardiovascular Devices 30-day notices and annual reports	FDA public workshop
	Other 2012	
September tba	**Vivus' Qnexa** (topiramate + phentermine) for obesity	EMA oral hearing
September 5	**Salix Pharmaceuticals' Provir** (crofelemer) for HIV-related diarrhea	PDUFA date (extended from June 5)
September 5	**Novartis' tobramycin inhalation powder** for management of cystic fibrosis patients infected with *Pseudomonas aeruginosa*	FDA's Anti-Infective Drugs Advisory Committee
September 8	**Ironwood Pharmaceuticals and Forest Laboratories' linaclotide** for irritable bowel syndrome	PDUFA date
September 10	**Navidea Biopharmaceuticals' Lymphoseek** (tilmanocept), a radioactive agent for tracing lymph nodes in cancer patients	PDUFA date (extended from June 10)
September 13	**Cornerstone Therapeutics/Cardiokine Biopharma's lixivaptan** for treatment of symptomatic hypervolemic and euvolemic hyponatremia associated with heart failure and syndrome of inappropriate antidiuretic hormone (SIADH) and **West-Ward Pharmaceutical's phenylephrine hydrochloride injection** to increase blood pressure in acute hypotensive states (e.g., shock and peri-operative hypotension)	FDA's Cardiovascular and Renal Drugs Advisory Committee
September 14	**Novartis' Gleevec** (imatinib) for adjunctive therapy of pulmonary arterial hypertension	FDA's Cardiovascular and Renal Drugs Advisory Committee
September 21	Classification of posterior **cervical screws**, including pedicle and lateral mass screws	FDA's Orthopaedic and Rehabilitation Devices Advisory Committee
September 23	**Regeneron's Eylea** (aflibercept) for central retinal vein occlusion (CRVO)	PDUFA date
September 27-28	Regulatory science considerations for performance validation of **radiation biodosimetry** devices	FDA public meeting
September 28	**Second Sight's Argus II Retinal Prosthesis System** for severe to profound retinitis pigmentosa	FDA's Ophthalmic Devices Advisory Committee
October 12	**Celgene's Abraxane** (nab-paclitaxel) to treat NSCLC	PDUFA date
October 21	**Impax Laboratories' IPX-066** for Parkinson's disease	PDUFA date
October 29	**Cornerstone Therapeutics' CRTX-080** to treat hyponatremia	PDUFA date
October 29-31	**Bayer's regorafenib** for metastatic CRC	PDUFA date
November 8	**Novo Nordisk's Tresiba** (degludec) **and Ryzodeg** (degludecPlus)	FDA's Endocrinologic and Metabolic Drugs Advisory Committee
November 14	Optimization of outcomes with **ventricular assist devices** (VADs) for patients with heart failure	CMS' MEDCAC
November 22	**Medivation** and **Astellas' enzalutamide** (MDV-3100) for castration-resistant prostate cancer	PDUFA date
November 29	**Exelixis' cabozantinib** to treat medullary thyroid cancer	PDUFA date
December 15	**Human Genome Sciences' raxibacumab** to treat anthrax	PDUFA date
December 21	**Alexa Pharmaceuticals' Adasuve** (loxapine) for agitation associated with schizophrenia or bipolar disorder	PDUFA date
December 28	**Biogen Idec's BG-12** for multiple sclerosis	PDUFA date

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
	2013	
January 17	**NuPathe's Zelrix** (transdermal sumatriptan), a migraine patch	PDUFA date
January 29	**Sanofi/Genzyme and Isis Pharmaceuticals' Kynamro** (mipromersen) for homozygous familial hypercholesterolemia	PDUFA date
January 30	**Raptor Pharmaceutical's cysteamine bitartrate** delayed-release (RP-103) to treat nephropathic cystinosis	PDUFA date
February 10	**Celgene's pomalidomide** for relapsed/refractory multiple myeloma	PDUFA date
February 24	**Dynavax's Heplisav** hepatitis B vaccine	PDUFA date
March 1	**Zogenix's Zohydro** (extended-release hydrocodone) for chronic pain	PDUFA date
April 11	**Sanofi/Genzyme and Bayer's Lemtrada** (alemtuzumab) for multiple sclerosis	PDUFA date