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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NOTE: Subscribe to ***Trends-in-Medicine*** for coverage of the **American Academy of Neurology** meeting in San Diego, details from the FDA's Circulatory Systems Devices Advisory Committee meeting on **Abbott Vascular's MitraClip Clip Delivery System (CDS)**, and details from the FDA's Psychopharmacologic Drugs Advisory Committee meeting on **Titan Pharmaceuticals' Probuphine** (buprenorphine hydrochloride + ethylene vinyl acetate), a subdermal implant for opioid dependence.

SHORT TAKES

- **ABBOTT VASCULAR's MitraClip Clip Delivery System (CDS) –** The FDA's Circulatory Systems Devices Advisory Committee voted unanimously (8-0) that the device is safe, 4-5 that it is effective, and 5-3 that its benefits outweigh risks. Separately, in a ***CRTonline*** survey, 67% of respondents said MitraClip should not be approved in the U.S. until after the ongoing COAPT trial is completed, and 33% said it should be marketed now.

- **AFFYMAX** fired 75% of its workforce (230 people) and is considering a sale or bankruptcy after the recall in February 2013 of **Omontys** (peginesatide) after three chronic kidney disease (CKD) patients on dialysis died from hypersensitivity reactions. Those deaths are still being investigated by Affymax and its marketing partner, **Takeda**, and if the reason is not able to be quickly identified, the drug may be permanently withdrawn from the market. Affymax also is considering restructuring itself into a much smaller company, which entails further layoffs.

- **AMGEN's talimogene laherparepvec (TVEC) –** The company announced that this investigational therapy, a genetically modified version of herpes simplex virus type 1, met the primary endpoint in a 400-patient Phase III trial in advanced melanoma. In the study, 16% of patients had significant tumor shrinkage that lasted at least six months vs. 2% of control patients treated with subcutaneous granulocyte-macrophage colony-stimulating factor (GM-CSF). Preliminary data also suggested a possible survival benefit.

- **Aspirin –** A study in Singapore, published in the ***British Journal of Ophthalmology***, found that aspirin use is associated with a greater risk for early age-related macular degeneration (AMD) in Asian Indians with cardiovascular disease but not in people with no history of cardiovascular disease. The authors found no clear explanation for the link.

- **ASTRAZENECA** is reorganizing its global research and development efforts. This includes cutting 1,600 employees over three years and moving its headquarters to Cambridge, U.K. Research will concentrate on three therapeutic areas – respiratory and inflammatory diseases, metabolic and cardiovascular disorders, and cancer – and will be focused in three locations: Cambridge,U.K.; Gaithersburg, MD; and Mölndal, Sweden.

- **BIOLINERX's BL-1020 –** The company stopped a trial vs. **Johnson & Johnson's Risperdal** (risperidone) in schizophrenia for futility after an early analysis found it was unlikely to meet its primary efficacy endpoint.

- **EISAI's eritoran (E-5564)**, an MD2-TLR4 antagonist, failed to improve survival in a study, published in the ***Journal of the American Medical Association***, in severe sepsis. The 28-day mortality was 28% with eritoran patients vs. 27% for placebo (p=0.59).

- **EVERYDAY HEALTH**, a health and wellness media company, is partnering with **Logical Images**, a health informatics company that manages the large visible light digital medical image library. Logical Images is the parent company of **Skinsight.com**, a dermatology-related online resource.

- **GLAXOSMITHKLINE's RTS –** A study published in the ***New England Journal of Medicine*** found that this investigational malaria vaccine becomes less effective over time. In Year 1, efficacy is 44%, but by Year 4 efficacy dropped to zero. However, the investigators found the vaccine prevents 65 cases of malaria for every 100 children vaccinated.

- **Hormone replacement therapy (HRT) –** A study published in the ***Canadian Medical Association Journal (CMAJ)*** suggested that gallstone disease should be added to the list of adverse events with use of menopausal HRT. The French researchers found that the highest risk for a cholecystectomy was associated with oral estrogen-only preparations. The study included data on 70,928 women followed for a mean of 11.5 years as part of the Étude Épidémiologique de femmes de la Mutuelle Générale de l'Éducation Nationale (E3N), a prospective cohort study.

- **INCYTE's Jakafi (ruxolitinib) –** The company notified the FDA and is investigating whether a 75-year-old man with myelofibrosis in the U.K. developed progressive multifocal leukoencephalopathy (PML) as a result of Jakafi. It is the only reported case of PML in the ~9,800 patients treated with Jakafi.

- **LIFE TECHNOLOGIES –** Since **Roche** was unsuccessful in its attempts to buy **Illumina**, it has now turned its sights on Life and has joined the bidding for this gene sequencing company. Other bidders include **Danaher Corporation**, **Thermo Fisher Scientific**, and others.

- **MERCK's Bridion (sugammadex) –** The FDA extended the review period by three months (now 2H13) for this investigational drug designed to reverse the effects of anesthesia.

- **NOVARTIS' LDK-378** was granted breakthrough therapy status by the FDA as a treatment for ALK+ metastatic non-small cell lung cancer (NSCLC) when **Pfizer's Xalkori** (crizotinib) can't be used.

- **OTSUKA PHARMACEUTICAL's Samsca (tolvaptan) –** Researchers reported in ***Clinical and Experimental Nephrology*** that this selective, competitive vasopressin receptor 2 antagonist used to treat hyponatremia may be an effective add-on diuretic for patients with CKD complicated by congestive heart failure (CHF).

- **PANASONIC** reportedly is considering "various options" for it healthcare unit, including selling it.

- **PHARMAXIS' Bronchitol (dry powder mannitol) –** The FDA rejected this inhaled therapy for cystic fibrosis, saying the company needed to conduct an additional study because "the submitted data do not provide a favorable benefit:risk balance." The FDA also expressed concern about safety, especially hemoptysis.

- **TITAN PHARMACEUTICALS' Probuphine (buprenorphine + ethylene vinyl acetate) –** The FDA's Psychopharmacologic Drugs Advisory Committee voted 12-2 (with 1 abstention) that this implant for treating opioid addiction is safe, 10-5 that it is effective, and 10-4 (with 1 abstention) that risk:benefit supports approval.

- **Renal denervation –** A survey by ***CRTonline*** found that 69% of respondents believe that renal denervation will be a niche procedure, and 31% believe it will be highly used.

- **VALEANT PHARMACEUTICALS** is buying **Obagi Medical Products**, further expanding its dermatology business.

- **WALGREENS** is switching drug distributors, giving its business to **AmerisourceBergen** when its current contract with **Cardinal Health** ends in August 2013.

NEWS IN BRIEF

GLP-1 agonists and DPP4 inhibitors – more on the risk of pancreatitis

Last week ***Quick Takes*** reported on the FDA's announcement that it is evaluating new, unpublished findings by academic researchers that suggested an increased risk of pancreatitis and pancreatic duct metaplasia in Type 2 diabetics treated with the whole class of incretin mimetic agents. This week, Public Citizen's Health Research Group reported some statistics that bear on this issue:

1. From January 1, 2010, to June 30, 2012, IMS prescribing data for the U.S. showed more than 35 million prescriptions were filled for another diabetes drug, glipizide, and 33 million prescriptions for the three top incretin mimetics –

Amylin's Byetta (exenatide), **Novo Nordisk's Victoza** (liraglutide), and **Merck's Januvia** (sitagliptin).

2. A Freedom of Information review of reports to the FDA's adverse reaction database (AERS) found 292 reports of pancreatic tumors in the same time period with the three incretin mimetics vs. 1 for glipizide.
3. In the "vast" majority of cases of pancreatic tumors in incretin patients, "the narrative…did not list any other possible causes of pancreatic cancers, such as a history of heavy alcohol intake or smoking."
4. There was a "substantial increase" in reports of pancreatic cancer for the three incretin mimetics in the last six months of the reporting period.

Public Citizen previously petitioned the FDA to ban Victoza because of concerns about pancreatic disease and thyroid cancer, but the watchdog group now believes all of the drugs in this family are associated with an increased risk of pancreatic cancer and believes all "will have to be removed from the market."

NOVO NORDISK

- **Victoza (liraglutide).** The company announced that a 56-week, 846-patient Phase IIIa trial of this diabetes drug helped diabetics lose weight as well as maintain glucose control. In the study, Victoza 3 mg patients lost 6% of their baseline weight vs. 5% for Victoza 1.8 mg and 2% for placebo patients.
- **NN-1954.** According to **Merrion Pharmaceuticals**, Novo Nordisk's partner on this oral insulin (which uses Merrion's **Gipet** technology), an 83-patient Phase I safety and tolerability trial was successful.

REGULATORY NEWS

FDA tells Congress about its plans for mobile apps

The FDA said it does not intend to regulate all mobile health applications. Instead, the Agency plans to focus on certain "higher risk" apps, such as those used by doctors and hospitals, that have the potential to put patients at risk if they do not work as intended. That's what Christy Foreman, director of the FDA's Office of Device Evaluation (ODE), Center for Devices and Radiological Health (CDRH), told a House Energy and Commerce subcommittee. She also said smartphones (iPhone, iPads, etc.) will not be subject to the medical device tax.

In an FDA blog, Foreman repeated what she had told the subcommittee, writing, "The FDA has no intention of stifling innovation in this rapidly growing field. The fact is, only a fraction of mobile apps would require FDA review. However, when a mobile app is doing the job of a medical device that requires FDA clearance or approval, it's only logical that both should be governed by the same rules."

Foreman said CDRH has been reviewing mobile medical apps for more than 10 years, "In that period we have reviewed about 100 applications, and each review has taken about 60 days to complete. We're confident that the center has the expertise to continue the timely review of the small number of submissions we expect to receive from mobile app developers."

Legislation may dictate hydrocodone status

Forty-two members of the House of Representatives have co-sponsored a bill, the Safe Prescribing Act, that would mandate that hydrocodone be changed from a Schedule III drug to a more restrictive Schedule II drug (along with oxycodone, fentanyl, and morphine). The FDA has been considering whether it would recommend the Drug Enforcement Administration (DEA) take this step, but apparently the legislators are tired of waiting for the FDA and DEA to act.

FDA requiring PMAs for automated external defibrillators (AEDs)

The FDA is taking the advice of its Circulatory Systems Devices Advisory Committee keeping AEDs as Class III devices but will require approval through the premarket application (PMA) process, not the less burdensome 510(k) pathway that has been used.

There currently are no AEDs that have PMA approval. That means, the seven manufacturers with AEDs on the market will have to submit PMAs for their products if they want them to stay on the market.

No devices are being removed from the market at this time. William Maisel, MD, MPH, deputy director of science and chief scientist at the FDA's CDRH, emphasized strongly that the FDA has confidence in the devices currently available, but the Agency wants to improve the quality and reliability of the devices going forward, "I want to make it clear that FDA is not questioning the clinical utility of AEDs…These devices are ***very*** important, and they serve a very important public health need …We also are not questioning the safety and reliability of the AEDs currently in distribution. [This] announcement does not require removal or replacement of current devices…We think AEDs are critically important devices with proven utility

and great value to society and public health. We believe they can be more reliable."

Between 2005 and 2012, the FDA received ~45,000 adverse event reports associated with AED failures, and there have been 88 device recalls. The Agency is unable to determine how many deaths are attributable to device failures. This sounds like a lot of adverse events, but Dr. Maisel said the failure rate is "significant" but "quite small."

Dr. Maisel said the problems with these devices have been preventable and correctable, and the Agency wants to avoid these issues in the future, particularly design and manufacturing issues or inadequate control of components purchased from outside suppliers. For example, problems have included devices powering off unexpectedly during a resuscitation attempt, error messages, and component failures that cause a device not to deliver a shock when the button is pushed.

Once the FDA order is finalized, the seven manufacturers with currently marketed AEDs will have 90 days to submit a notice to the FDA that they intend to submit PMAs. Then, they will have 15 months to complete their submissions.

Under a PMA, the FDA reviews not only data on clinical safety and effectiveness but also a manufacturer's quality systems information and inspects the manufacturing facilities. After a PMA approval, manufacturers must submit to the FDA any significant manufacturing changes made to the devices as well as annual reports on the device's performance. Dr. Maisel said, "A PMA…allows us to focus on the types of [issues] we have seen."

How burdensome will this be for the seven affected manufacturers? Dr. Maisel said there will be a one-time fee of $240,000 per manufacturer that will cover all that firm's models, plus another $4,000 for each supplement (future iteration/modification/change). However, Dr. Maisel does not think the clinical data will be a problem, "We have looked at the clinical data available, and we are reaching out to each individual company to let them know what we expect will need to be filed with their PMA. The companies will be required to submit clinical data with their PMA submission, but based on our review, we believe the vast majority of companies have already collected that clinical data…So, we don't think many, if any, companies will be required to conduct clinical trials."

The FDA is accepting comments on the proposed order for 90 days.

FDA's Office of Generic Drugs gets *another* acting director

When Greg Geba, MD, MPH, announced last week that he was abruptly leaving as head of the FDA's Office of Generic Drugs (OGD), Janet Woodcock, MD, director of the FDA's Center for Drug Evaluation and Research (CDER), said she would be the acting director until a replacement for Dr. Geba was found.

However, Dr. Woodock's term as the acting director of OGD was very short lived. This week, she named Kathleen Uhl, MD, the new acting director. Dr. Uhl, a clinical pharmacologist, has been with the FDA for 15 years, most as senior advisor to Dr. Geba, and before that deputy director of the Office of Medical Policy.

Dr. Woodcock praised Dr. Uhl's "strong management skills and extensive expertise in clinical pharmacology" and said she was "instrumental" in the FDA's negotiations with industry for the authorization of the new Biosimilar User Fee Act of 2012 (BsUFA).

Will new compounding rules affect access to Avastin?

Access to **Roche/Genentech's compounded Avastin** (bevacizumab) for intravitreal injections to treat age-related macular degeneration (AMD) got tighter after the meningitis outbreak tied to New England Compounding Center (NECC), and as state and federal regulators increase their oversight of compounding, the situation is getting tougher. So far, retinal specialists are not reporting an inability to get Avastin, but their sources have been drying up.

FDA Commissioner Margaret Hamburg, MD, wrote in an FDA blog this week about the need for new legislation (and funding) for the FDA to oversee compounding pharmacies, and one comment in that blog again raises the question of whether Avastin will continue to be able to be compounded. Dr. Hamburg wrote that one "basic protection" should be "prohibiting compounding of the most complex and highest risk products – drugs and biologics that should only be made for patients by an FDA-registered drug manufacturer under an approved new drug application."

Meanwhile, the Senate Health, Education, Labor, and Pensions (HELP) Committee continues to work on compounding oversight legislation. A white paper was expected in April 2013, but initial timelines are proving overly optimistic. It now looks like it will be later this spring.

FDA approvals/clearances

- **ABBVIE's AndroGel 1.62%**, a topical testosterone formulation in a pocket-size pack, was approved to treat men with hypogonadism.
- **EOS IMAGING's sterEOS version 1.5**, software for 3D x-ray imaging, received 510(k) clearance.
- **GUERBET's Dotarem (gadoterate meglumine)**, a gadolinium-based contrast agent for use in magnetic resonance imaging, was approved.
- **LANTOS TECHNOLOGIES' 3D ear scanning system** was cleared for use, but the company does not plan to launch it until later this year. The system allows for the development of hearing aid devices that are customized to each patient by making it easier to measure ear topology.
- **MERIDIAN BIOSCIENCE's illumigene Group A and Group B *Streptococcus* tests** received CLIA moderate complexity ratings. They already were cleared for use but were previously classified as high complexity tests.
- **NOVARTIS' TOBI Podhaler (tobramycin inhalation powder)**, a hand-held dry powder inhaler, was approved for the management of cystic fibrosis patients with *Pseudomonas aeruginosa*, a bacterium that causes lung infections.
- **QUANTEL MEDICAL's Vitra Multispot Laser System**, which uses pattern scanning technology to help ophthalmologists detect diabetic retinopathy, received 510(k) clearance.
- **QUIDEL's Molecular Direct *C. difficile* Assay**, for use with the 7500 Fast Dx Applied Biosystems Real-Time PCR Instruments and QuantStudio Dx from Life Technologies, was cleared for use.
- **SYNCARDIA SYSTEMS' 50cc Total Artificial Heart** was granted two humanitarian use device exemptions: one as a bridge-to-transplant for pediatric patients and other people with small stature and another as destination therapy for heart failure patients at risk of imminent death.
- **X-SPINE's Silex system** was cleared for sacroiliac joint fusion.

FDA recalls/warnings

- **APOTEX** received a warning letter about violations of current Good Manufacturing Practice (cGMP) at its plant in Canada that manufactures these products.
- **CLINICAL SPECIALTIES** (a Georgia compounder) recalled all **compounded Avastin** (unit-dose syringes) used for treating age-related macular degeneration due to lack of sterility assurance. Five patients reportedly have developed serious eye infections after intravitreal injections with the company's compounded Avastin.
- **INTEGRA LIFESCIENCES' Absorbable Collagen Sponges and DuraGen Collagen products** – The company received a warning letter about violations of cGMP at the plant in Puerto Rico that manufactures these products.
- **MED PREP CONSULTING** (a New Jersey compounder) recalled all lots of its compounded products due to mold contamination, and the company will remain closed until at least April 5, 2013.
- **NUVASIVE's Affix Spinous Process Plate System** – The company received a warning letter over marketing language for this spinal implant. NuVasive was marketing the device as "an adjunct to interbody fusion (XLIF, ALIF, PLIF, and TLIF)," a claim that the FDA said requires a new 510(k) clearance because none of the "multiple" 510(k) clearances that the device has covered that claim.
- **SYMBIOS MEDICAL PRODUCTS' GOPump Elastomeric Infusion PumpKit** – A Class I recall was initiated, and the company sent its customers an "Urgent Medical Device Recall" notification letter explaining that the recall is due to a flow restrictor bead that may become displaced from its fitting, permitting solutions to flow at a higher rate than intended, which could cause serious adverse events, including death.
- **VASCULAR SOLUTIONS/ZERUSA's Guardian II and Guardian II NC hemostasis valves** were recalled due to a slightly increased risk of air leakage that could lead to an air embolism, which could result in serious injury or death.

European regulatory news

- **ACTIVARTIS' AV-0113**, a cancer immunotherapy, was granted orphan drug status for treating glioma by the European Medicines Agency (EMA).
- **BAXTER and HALOZYME THERAPEUTICS' HyQvia** (human normal immunoglobulin with recombinant human hyaluronidase) – The EMA's Committee for Medicinal Products for Human Use (CHMP) recommend approval of this treatment for primary and secondary immunodeficiencies.
- **INSPIREMD's MGuard** received a CE Mark for the prevention of blood clots that may cause stroke in patients who have undergone a coronary stent procedure.
- **NOVARTIS/ALCON's Jetrea (ocriplasmin)** was approved by the European Commission for the treatment of vitreomacular traction linked to macular holes.

- **ROCHE's Pegasys (pegylated interferon alfa-2a)** + ribavirin received expanded approval to treat chronic hepatitis C to include children age ≥5 years.

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

NOVARTIS' Afinitor (everolimus), a breast cancer drug, was rejected over concerns about its survival benefits.

Regulatory news from other countries

- ***Brazil:*** **FAXITRON's BioVision system** for intraoperative specimen radiography and its CoreVision stereotactic core biopsy specimen radiography technology were approved by the Agência Nacional de Vilgilância Sanitária.
- ***Canada:***
  - Health Canada issued final guidelines for classifying therapeutic products as drugs or devices. The guidance says that a product cannot be considered both a device and a drug.
  - The Canadian pharmaceutical trade association, Research-Based Pharmaceutical Companies, criticized the price limit set by Quebec's health services review agency for proton pump inhibitors.
- ***China:***
  - The State Food and Drug Administration said that anti-infection medications accounted for ~40% of the 1.2 million adverse drug reactions in China last year, with 81.6% of adverse drug reactions due to chemical-based medicines and 17.1% from traditional Chinese medical treatments. However, the risk represented a decrease in the proportion of adverse reactions due to anti-infection drugs.
  - **ETVIEW MEDICAL's VivaSight-SL system**, a single-use ventilation tube and a small camera to assist doctors with lung isolation when performing pulmonary surgeries, received premarket approval.

2013 FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
March 28	**Biogen Idec's BG-12** (dimethyl fumarate) for multiple sclerosis	PDUFA date (extended from December 28, 2012)
March 31	**United Therapeutics' oral treprostinil** to treat pulmonary artery hypertension	PDUFA date
March 31	**Johnson & Johnson's Invokana** (canagliflozin), a SGLT2 inhibitor to treat Type 2 diabetes	PDUFA date
April 8	**Bausch & Lomb's Trulign Toric** implantable intraocular lens for post-cataract surgery patients	FDA's Ophthalmic Devices Advisory Committee
April 11	Potential effects of extreme weather and natural disasters on **medical device safety and quality**	FDA's Device Good Manufacturing Practice Advisory Committee
April 15	**MAP Pharmaceuticals' Levadex** (dihydroergotamine), inhaled migraine drug	PDUFA date
April 25	Reclassification of **methotrexate enzyme immunoassays, phencyclidine (PCP) enzyme immunoassays, and PCP radioimmunoassays**	FDA's Clinical Chemistry and Clinical Toxicology Devices Advisory Committee
April 26	Reclassification of **isoniazid test strips**	FDA's Clinical Chemistry and Clinical Toxicology Devices Advisory Committee
April 29	**Shire's Vyvanse** (lisdexamfetamine dimesylate), sNDA for ADHD treatment in children	PDUFA date
April 29-30	Discussion of **medical device labeling standardization**, including an online labeling repository for in-home medical devices	FDA public workshop
April 30	**Raptor Pharmaceutical's Procysbi** (cysteamine bitartrate delayed-release, RP-103) to treat nephropathic cystinosis	PDUFA date (extended from January 30, 2013)
April 30	**Titan Pharmaceuticals' Probuphine** (buprenorphine implant) for opioid dependence	PDUFA date
May 2	**Allergan's Juvéderm Voluma XC**, a facial filler with hyaluronic acid and lidocaine	FDA's General and Plastic Surgery Devices Advisory Committee
May 2	**Aveo and Astellas' Tivopath** (tivozanib) for advanced renal cell carcinoma	FDA's Oncologic Drugs Advisory Committee
May 12	**GlaxoSmithKline** and **Theravance's Breo/Relvar** (fluticasone furoate + vilanterol) to treat chronic obstructive pulmonary disease (COPD)	PDUFA date
May 31	**Depomed's Sefelsa** (gabapentin extended-release), a hot-flash treatment (formerly known as Serada)	PDUFA date
June 20	**Dainippon Sumitomo Pharma/Sunovion Pharmaceuticals' Latuda** (lurasidone), a schizophrenia drug for use in treating bipolar disorder	PDUFA date
June 28	**Hisamitsu Pharmaceutical/Noven Pharmaceuticals' Pexeva** (paroxetine mesylate), a low-dose SSRI antidepressant to treat non-hormonal hot flashes in menopausal women	PDUFA date
July tba	**PET imaging** of brain beta-amyloid	CMS coverage decision expected
July 28	**Aveo Oncology** and **Astellas Pharma's Tivopath** (tivozanib) to treat advanced renal cell carcinoma	PDUFA date
August 17	**ViiV Healthcare's dolutegravir** for HIV	PDUFA date
September tba	**Sanofi/Genzyme's Lemtrada** (alemtuzumab) for multiple sclerosis	PDUFA date
October 2	**Lundbeck** and **Takeda's Brintellix** (vortioxetine), an antidepressant for major depressive disorder	PDUFA date
October 3	**Pfizer** and **Ligand Pharmaceuticals' Aprela** (bazedoxifene/conjugated estrogens) to treat menopausal symptoms and osteoporosis prevention	PDUFA date
October 19	**Actelion's Opsumit** (macitentan), a dual endothelin receptor antagonist to treat pulmonary arterial hypertension	PDUFA date
October 21	**AMAG Pharmaceuticals' Feraheme** (ferumoxytol) expanded indication	PDUFA date
October 28	**Neos Therapeutics' NT-0202** (extended-release tablet formulation of amphetamine polistirex) to treat ADHD	PDUFA date
December 18	**GlaxoSmithKline** and **Theravance's Anoro** (umeclidinium bromide + vilanterol) for COPD	PDUFA date