TRENDS-in-MEDICINE

**December 11, 2011**

*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

- **AVEDRO's VibeX (riboflavin ophthalmic solution)**, an investigational therapy to treat corneal ectasia after refractive surgery, was granted orphan drug status by the FDA. The company said it plans to submit the drug to the FDA for approval in 1Q12.
- **BOEHRINGER INGELHEIM's Pradaxa (dabigatran) –** The FDA is investigating post-marketing reports of serious bleeding events reported with this oral direct thrombin inhibitor approved for prevention of stroke in AFib patients. The FDA noted that bleeding is in the drug's label but said it wants to determine whether the bleeding is occurring at an excess rate. The company has insisted the bleeding is in the expected range.
- **COOPERVISION's Avaira –** The FDA raised the recall on these silicone hydrogel contact lenses to a Class I recall. The FDA warned doctors and patients that anyone wearing these lenses should stop wearing them immediately. The problem is the same as previously reported – "unintended [silicone oil] residue on the lenses."
- **EMERGENT BIOSOLUTIONS' TRU-016**, an investigational treatment for chronic lymphocytic leukemia (CLL), received orphan drug status from the FDA. It is also under investigation in non-Hodgkin's lymphoma.
- **Generic epilepsy medications –** An FDA official told doctors at the American Epilepsy Society meeting that it is studying the issue of varying efficacy of generic antiepileptic drugs, which have a narrow therapeutic index, and is considering tightening controls on some of them.
- **MOMENTA PHARMACEUTICALS** is buying **Virdante Pharmaceuticals**' sialic switch assets, a technology used to treat autoimmune and inflammatory disorders.
- **NEOPROBE**, which already sold its top revenue source – a hand-held gamma radiation detector business – to **Devicor Medical Products**, is changing its name to **Navidea Biopharmaceuticals** to reflect its move into diagnostic pharmaceuticals.
- **PROTALIX BIOTHERAPEUTICS' taliglucerase alfa –** The FDA extended its review period for this investigational Gaucher disease drug that would compete with **Genzyme's Cerezyme** (imiglucerase) by three months. However, the company said the FDA did not request additional data. The new PDUFA date is May 1, 2012.
- **RIVERAIN TECHNOLOGIES' OnGuard 5.2**, an advanced version of the company's imaging system that "suppresses" a patient's bones to diagnose lung cancer, was approved by the FDA.

- **WARNER CHILCOTT's Asacol (mesalamine)** – Responding to a petition by Warner Chilcott, the FDA said it will require any generic mesalamine to prove it is bio-equivalent to brand Asacol.

## NEWS IN BRIEF

### Antidepressants – newer antidepressants have pretty equal efficacy

A meta-analysis of 234 randomized studies – published in the ***Annals of Internal Medicine*** and funded by the Agency for Healthcare Research and Quality – found newer antidepressants are all equally effective. However, there were differences in onset of action, side effects, and quality of life.

- **GlaxoSmithKline's Wellbutrin (bupropion)** was linked with less sexual dysfunction than **Forest Laboratories' Lexapro** (escitalopram), **GlaxoSmith-Kline's Paxil** (paroxetine), **Lilly's Prozac** (fluoxetine), or **Pfizer's Zoloft** (sertraline).
- **Pfizer's Effexor (venlafaxine)** had an increased risk of nausea.
- **Organon's Remeron (mirtazapine)** had more weight gain than **Forest Laboratories' Celexa** (citalopram), Paxil, Prozac, or Zoloft.
- **Remeron** worked faster than Celexa, Paxil, Prozac, or Zoloft.

### BAYER

- **Betaseron (interferon-beta-1b).** In what could be a game changing move, Bayer cut a deal with an Illinois insurer (Health Alliance Medical Plans) under which Bayer indemnified the insurer against certain hospitalization costs. Under the agreement, if a multiple sclerosis (MS) patient taking Betaseron as directed is hospitalized for a severe MS relapse, Bayer will pay for that hospitalization. *What does the insurer have to lose? It's an interesting strategy.*
- **Yasmin or Yaz (progestin drospirenone).** The FDA's Reproductive Health Drugs Advisory Committee, meeting jointly with the Drug Safety and Risk Management Advisory Committee, offered a weak endorsement of continued use of these oral contraceptives, voting 15-11 that their benefits outweigh the risk of venous thromboembolism (VTE). The panel also recommended 21 to 5 that the labels for both products be revised to include stronger safety warnings, but it did not recommend the label say Yaz and Yasmin are more likely than other oral contraceptives to cause blood clots.

  However, a ***Bloomberg News*** survey found that gynecologists still plan to prescribe these products.

### GE and MICROSOFT – collaborating on healthcare IT

General Electric and Microsoft plan to combine Microsoft systems that use information for billing and patient privacy protocols with GE's live hospital and patient data system in a so-far unnamed joint venture. According to ***Modern Healthcare***, GE Healthcare's IT connectivity business unit – which includes GE's health information exchange, a clinical knowledge project, and the imaging exchange – will be part of the venture. Microsoft's contribution will be its enterprise health intelligence platform, context management technology, and single sign-on tool. The CEO will be Michael Simpson, vice president and general manager of GE Healthcare IT.

### JOHNSON & JOHNSON

- J&J is buying the rights to **Pharmacyclics' PCI-32765**, a drug under investigation to treat a variety of cancers, including non-Hodgkin's lymphoma.
- **Ortho Evra (norelgestromin/ethinyl estradiol transdermal patch).** The FDA's Reproductive Health Drugs Advisory Committee, meeting jointly with the Drug Safety and Risk Management Advisory Committee, voted 19-5 that the benefits of this contraceptive patch outweigh potential blood clot risks, but panel members recommended strengthening the label warnings.

### MEDTRONIC's CRT-Ds – FDA panel neutral on use in less severe heart failure

The FDA's Circulatory System Devices Advisory Committee was split on whether to recommend approval of the company's cardiac resynchronization therapy with cardioverter defibrillator devices (CRT-Ds) in patients with mildly symptomatic heart failure. The devices are already approved for patients with moderate-to-severe heart failure. The panel voted 5-0 that the devices are safe, 3-2 that they are effective in patients with mild symptomatic heart failure, and 3-2 that the overall risk:benefit profile is positive. The FDA generally considers close votes to be neutral.

### News from the International Conference on Cancer-Induced Bone Disease:

- **Amgen's Xgeva (denosumab)**
  - Patients with giant cell tumor of bone had a near-total absence of disease progression during treatment with Xgeva. The investigators reported that all but one of 96 patients had stable disease or better, including objective responses in almost half of the patients. In addition, in the 23-patient subgroup with surgically salvageable

disease, 15 avoided surgery and five others had less extensive surgery than originally planned.

- Osteonecrosis of the jaw (ONJ) is infrequent in cancer patients treated with Xgeva (2%), but researchers said the rate appears to increase over time in some subgroups, notably prostate cancer and breast cancer patients.

- **Novartis' Zometa (zoledronic acid).** Overall survival was significantly improved in patients getting Zometa (a bisphosphonate) as well as **Celgene's Thalomid** (thalidomide) as induction treatment vs. Thalomid alone. In addition, the Zometa patients had fewer skeletal-related events (SREs) vs. patients who received other chemotherapy + clodronate.
- **TGF-beta inhibition** failed to show a benefit in a pre-clinical mouse model of myeloma. Most of the mice developed metastases despite treatment with the TGF-beta inhibitor antibody 1D11 vs. one mouse in control.

### Platelet drugs – REMS loosened

The FDA has eliminated the requirement that clinicians, patients, medical facilities, and pharmacies enroll in a special-access program for **Amgen's Nplate** (romiplostim) and **GlaxoSmithKline's Promacta** (eltrombopag). Both drugs are used to treat adults with chronic immune thrombocytopenia. The FDA determined that safety risks still exist for these agents, but this requirement of the risk evaluation and mitigation strategy (REMS) is no longer necessary.

### Prostate cancer – active surveillance gets NIH recommendation

A National Institutes of Health consensus panel backed active surveillance in lieu of immediate surgery or radiation treatment for men with low-risk prostate tumors. In a draft statement, the 14-member panel said treating low-risk patients with radical prostatectomy or radiation can cause side effects such as impotence and incontinence, making active surveillance "a viable option that should be offered to low-risk patients."

The panel also recommended renaming low-risk prostate cancer something without the "anxiety-provoking" term "cancer" in it. Low risk was defined as:

- Tumor stage of T1c if PSA-detected or T2a if a small, palpable nodule.
- PSA <10 ng/mL.
- Gleason score ≤6.
- Extent of disease on biopsy.

### SANOFI

- **Sanofi and UCB's Xyzal (levocetirizine).** A blinded, placebo-controlled study reported in the ***Annals of Allergy, Asthma, and Immunology*** found Xyzal was ***not*** less sedating – and had no added efficacy – vs. cetirizine.
- **Sanofi and Zealand Pharma's Lyxumia (lixisenatide)**, a once-daily GLP-1 agonist, reduced blood-sugar levels after meals more than **Novo Nordisk's Victoza** (liraglutide) in patients whose glucose was not adequately controlled with metformin. The top-line data from the Phase III GetGoal-M trial was reported at the World Diabetes Congress in Dubai. Lyxumia was submitted to European regulators on November 16, 2011, and an FDA submission is expected in 4Q12.

### SHIRE's ProAmatine (midodrine) – two new trials to be conducted

Shire agreed to conduct two more clinical trials of this low blood pressure medication so generic versions can remain on the market. ProAmatine was given accelerated approval by the FDA in 1996, but additional studies were required. Shire did two additional studies and submitted them in 2005, but the FDA wanted additional data. By then, however, the drug had gone off patent, and Shire no longer wanted to do more studies, preferring to withdraw the drug from the market, but that would also have meant generic versions would have to be removed from the market.

After negotiating with the FDA, Shire agreed to these new trials, which are expected to be completed by 2014. Generic midodrine will remain available at least until then.

## REGULATORY NEWS

### HHS overrode FDA decision on Plan B One-Step

Health and Human Services (HHS) Secretary Kathleen Sebelius pulled rank on FDA Commissioner Margaret Hamburg, MD, and ordered Dr. Hamburg to reject lowering the age limit for **Teva's Plan B One-Step** (the morning-after emergency contraceptive with levonorgestrel). This is the first known time that an FDA decision has been overridden by the HHS Secretary in the history of the FDA.

Plan B One-Step was originally approved in July 2009 for use without a prescription by females age 17 and up and as a prescription-only option for females <age 17. In February 2011, Teva Women's Health submitted a supplemental application seeking to remove the prescription-only status for

females younger than age 17 and to make Plan B One-Step non-prescription for all females of child-bearing potential.

The FDA's Center for Drug Evaluation and Research (CDER) determined the product was safe and effective in adolescent females, that adolescent females understood the product was not for routine use, and that they understood it would not protect them against sexually transmitted diseases. CDER also found that adolescent females could use Plan B One-Step properly without the intervention of a healthcare provider.

Dr. Hamburg said CDER's decision was based on scientific evidence: "I agree with the Center [CDER] that there is adequate and reasonable, well-supported, and science-based evidence that Plan B One-Step is safe and effective and should be approved for non-prescription use for all females of child-bearing potential."

However, Sebelius ordered Dr. Hamburg not to approve Plan B One-Step and to issue a complete response letter instead. Dr. Hamburg said Sebelius invoked her authority under the Federal Food, Drug, and Cosmetic Act to execute its provisions, "stating that she does not agree with the Agency's decision to allow the marketing of Plan B One-Step non-prescription for all females of child-bearing potential…[This means] that the supplement for non-prescription use in females under the age of 17 is not approved."

President Obama publicly backed Sec. Sebelius' decision.

Certainly, Plan B has been politically controversial, but Sebelius' action politicizes the FDA in a dramatic way. The FDA is supposed to be above politics, making science-based decisions. *Are politicians now to make decisions on the safety and effectiveness of drugs?*

*And this is not the only example of HHS interference with the daily operations of the FDA. FDA sources indicate that HHS routinely meddles in Agency business, though not at the level of the Plan B action.*

## FDA defends its drug approval record but offers some improvements for PDUFA-V

Speaking at the FDA/CMS Summit for Biopharma Executives, John Jenkins, MD, director of the FDA's Office of New Drugs, CDER, defended the Agency's approval rate for new drugs. He said the FDA is meeting "nearly all our PDUFA goals for application review."

Dr. Jenkins insisted that FDA officials do not interfere with the speed of the approval process, "In my 19½ years at FDA, I have never received or issued an order to 'speed up' or 'slow down' on drug approvals. We do not have goals for numbers of approvals by year, by division, etc."

So far in 2011, Dr. Jenkins said the FDA has approved 30 NMEs, the highest number since 2004. Twelve were first-in-class, "many" were breakthrough therapies, half received priority review, and a record number (14) had fast track status. He insisted that CDER did not "slow down" NME applications in the last half of this year, adding, "We cannot approve more NME applications than are submitted!"

Nearly one-third (11) of the NMEs approved this year were for rare diseases and were submitted by "emerging" sponsors, not big pharma – e.g., Incyte, Seattle Genetics, and Shire. These smaller companies pose additional challenges to the FDA and the approval process, Dr. Jenkins said, because:

- Inexperienced sponsors need more advice and meetings with the FDA.
- They may interpret an FDA statement that something is a "review issue" as "that will be just fine."
- They are more likely to submit formal dispute resolution requests because that is "quicker, less expensive, and more 'promising' than conducting new trials, but the success rate is low."

Dr. Jenkins said the FDA has listened to stakeholder concerns expressed at public meetings and considered those issues in preparing its proposals for PDUFA-V for FY2013-2021, which are expected to be finalized in January 2012. These proposals are designed to address some specific problems, and Dr. Jenkins said that, among them, the FDA is proposing holding a number of public meetings to discuss things like:

- Complex issues in clinical trials for drugs for rare diseases.
- Strategies to facilitate scientific exchanges in both regulatory and non-regulatory contexts.
- A review with patient advocacy groups of available therapies for rare diseases.
- Patient-reported outcome endpoints in Phase III trials.
- Approaches to meta-analyses.
- The effectiveness, impact on patient access, and burden on the healthcare system of REMS.

## FDA approvals/clearances

- **AGAMATRIX's iBGStar**, also known as the AgaMatrix Nugget, the first glucose meter available on iPhones, was granted 510(k) clearance. **Sanofi**, which has been marketing the device in Europe, also will handle marketing in the U.S.
- **ANTARES PHARMA and WATSON PHARMACEUTICALS' oxybutynin 3% topical gel** was approved to treat overactive bladder patients with symptoms of urinary incontinence, urgency, and frequency. It is applied QD in a dose of 84 mg to the thigh, abdomen, upper arm, or shoulder through a metered-dose pump.
- **BOSTON SCIENTIFIC's Infinion 16**, a percutaneous lead with more contacts, was approved for use with the company's Precision Plus spinal cord stimulator device to treat chronic pain.
- **MAZOR ROBOTICS' Renaissance** – The FDA approved the addition of 3D imaging functions to this surgical robot that replaces the company's SpineAssist System.
- **TEARLAB's TearLab Osmolarity System** – The FDA expanded use to include detection of dry eye disease.
- **X-SPINE's Axle-PEEK**, a spinal fusion device for degenerative disk disease, received 510(k) clearance.

## FDA recalls and warning letters

- **AKZO NOBEL CHEMICALS** got a warning letter from the FDA saying its active pharmaceutical ingredient (API) plant in Mexico does not meet cGMP, and the company's correction actions are not sufficient.
- **BECKMAN COULTER** got a warning letter from the FDA saying its Florida *in vitro* diagnostic manufacturing facility did not meet cGMP, and the FDA could not determine yet if corrective actions the company has taken are adequate.
- **NOVARTIS/SANDOZ** got a warning letter from the FDA after inspections of the Sandoz plants in Colorado, North Carolina, and Canada found "significant violations" of cGMP, including contamination, failure to meet specifications on a batch, inadequate validation testing, and failure to file required reports. The FDA also has not been satisfied with the company's corrective actions.

## European regulatory actions

- **BAUSCH + LOMB and TECHNOLAS PERFECT VISION's Victus** femtosecond laser platform received a CE Mark.
- **RAYNER's Sulcoflex Multifocal Toric IOL** received a CE Mark. The company plans to launch it in 1Q12.
- **SORIN's Inspire 6**, an adult oxygenator device used in conjunction with a heart-lung machine during cardiopulmonary bypass operations, was granted a CE Mark. The company plans to launch the device in 1H12.
- **TAKEDA's Edarbi (azilsartan medoxomil)**, an ARB for hypertension, was approved for once-daily use.

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

**MERCK's Daxas (roflumilast)** – NICE asked Merck to conduct another trial of this drug for chronic obstructive pulmonary disease (COPD) in combination with other commonly used treatments to prove the drug offers an advantage. NICE said there is a lack of evidence for Daxas in combination with bronchodilator treatments.

| Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*) | | |
|---|---|---|
| **Date** | **Topic** | **Committee/Event** |
| | **December 2011** | |
| December tba | **Allergan's brimonidine tartrate intravitreal implant** – Phase II trial in dry AMD to be completed | Company announcement or medical conference presentation |
| December 12 | **Alexza Pharmaceuticals' Adasuve** (loxapine inhalation powder) for the acute treatment of agitation associated with schizophrenia or bipolar I disorder in adults. Pulmonary safety is the key concern. | FDA's Psychopharmacologic Drugs Advisory Committee |
| December 13 | **Endo Pharmaceuticals' Opana** (extended-release oxymorphone) for pain | PDUFA date |
| **December 16** | Approval pathway for **biosimilar drugs** | FDA public meeting |
| | **January 2012** | |
| January | **Pfizer's Prevnar 13** (PCV13), a pneumococcal vaccine for adults | PDUFA date |
| January 3 | **Medical device labeling** feedback is sought | FDA deadline for public comment |
| January 11 | **Torax Medical's LINX Reflux Management System** to treat the symptoms associated with gastroesophageal reflux disease (GERD) | FDA's Gastroenterology and Urology Devices Advisory Committee |
| January 20 | Efficacy of **Columbia Laboratories' progesterone gel 8%** to reduce the risk of preterm birth in women with short uterine cervical length | FDA's Reproductive Health Drugs Advisory Committee |
| January 28 | **Bristol-Myers Squibb and AstraZeneca's dapagliflozin**, a first-in-class SGLT2 inhibitor for Type 2 diabetes | PDUFA date |
| January 28 | **Eli Lilly, Amylin Pharmaceuticals and Alkermes' Bydureon** (weekly exenatide XR), an injectable drug for Type 2 diabetes | FDA decision date |
| | **February 2012** | |
| February | **Alcon's tandospirone** for dry AMD – Phase III final data expected | Company announcement or medical conference presentation |
| February 4 | **Alexza Pharmaceuticals' Adasuve** (loxapine inhalation powder) for the acute treatment of agitation associated with schizophrenia/bipolar I disorder | PDUFA date |
| February 10 | Possible reclassification of **cranial electrotherapy stimulator (CES) devices** to Class III (requiring a PMA) | FDA's Neurological Devices Advisory Committee |
| February 17 | **Corcept Therapeutics' Corlux** (mifepristone) for Cushing's syndrome | PDUFA date |
| February 27 | Review of evidence needed for approval of **anti-inflammatory ophthalmic drugs post-ocular surgery** and appropriateness of marketing a single bottle for use in both eyes post-surgery | FDA's Dermatologic and Ophthalmic Drugs Advisory Committee |
| February 28 | **Pfizer's axitinib** for advanced renal cell carcinoma | PDUFA date (*approximate*) |
| | **March 2012** | |
| March tba | **Anti-nerve growth factor (NGF)** drug class safety review | FDA's Arthritis Advisory Committee – originally scheduled for September 13, 2011, but postponed indefinitely, now March 2012 |
| March 6 | **Discovery Labs' Surfaxin** (lucinactant) for infant respiratory disease | PDUFA date |
| March 7 | **NeurogesX' Quetenza** (transdermal capsaicin) for HIV-related neuropathic pain | PDUFA date |
| March 8 | **Roche/Genentech and Curis' vismodegib** for advanced basal cell carcinoma in adults for whom surgery is not an option | PDUFA date |
| March 27 | **Affymax and Takeda's peginesatide** for anemia | PDUFA date |
| March 28 | **Bristol-Myers Squibb's Eliquis** (apixaban) to prevent strokes in AFib | PDUFA date |
| March 28 | **Chelsea Therapeutics' Northera** (droxidopa) for symptomatic neurogenic orthostatic hypotension with primary autonomic failure | PDUFA date |
| March 28 | **Edwards Lifesciences' Sapien** transcatheter aortic valve | CMS expected to publish NCD decision memo |
| | **April 2012** | |
| April 17 | **Vivus' Qnexa** (phentermine + topiramate) for weight loss | PDUFA date for resubmission |
| **April 24** | **Cell Therapeutics' pixantrone** for aggressive non-Hodgkin's lymphoma | PDUFA date |
| April 25 | **Takeda's alogliptin**, a DPP-4 for Type 2 diabetes | PDUFA date |
| April 26 | **Amgen's Xgeva** (denosumab) for prevention/delay of bone metastases in prostate cancer | PDUFA date |
| April 27 | **Salix Pharmaceuticals and Progenics Pharmaceuticals' Relistor** (methylnaltrexone injection) for opioid-induced constipation | PDUFA date |
| April 29 | **Vivus' avanafil** for erectile dysfunction | PDUFA date |
| April 30 | **Baxter and Halozyme's HyQ** for immunodeficiency | PDUFA date |
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| Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*) | | |
|---|---|---|
| **Date** | **Topic** | **Committee/Event** |
| | **Other 2012** | |
| **May 1** | **Protalix Biotherapeutics' taliglucerase alfa**, an investigational Gaucher disease drug | ***New*** PDUFA date |
| June | **Forest Laboratories and Ironwood Pharmaceuticals' linaclotide** for IBS-C | PDUFA date |
| June 25 | **QRxPharma's MoxDuo** (morphine + oxycodone) | PDUFA date |
| June 26 | **Edwards Lifesciences' Sapien** transcatheter aortic valve | CMS final NCD expected |
| July 26 | **Amarin's AMR-101** (omega-3 fish oil EPA) to treat hypertriglyceridemia | PDUFA date |
| July 26 | **Horizon Pharma's Lodotra** (low-dose prednisone) for rheumatoid arthritis | PDUFA date |
| July 30 | **Regeneron's Arcalyst** (rilonacept) for gout | PDUFA date |
| August | **Pfizer's tofacitinib,** an oral JAK2 inhibitor for rheumatoid arthritis | PDUFA date |