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

- **BAYER's Alpharadin (radium-223 chloride)** – The FDA approved an expanded-access program to allow use of this alpha-emitting radiotherapy in men who are not eligible for clinical trials in metastatic castration-resistant prostate cancer (CRPC).

- **BRISTOL-MYERS SQUIBB's FGF-21** – BMS bought the rights to **Ambrx's** preclinical **Fibroblast Growth Factor 21** (FGF-21), a potential diabetes therapy, in September 2011, and it looked very promising at the time. However, two new mouse studies suggest that it may not be safe. A study published in the journal ***Cell*** found that FGF-21 burns fat but causes bone loss in mice. Another study, published in the ***Proceedings of the National Academy of Sciences***, found that mice given the drug for two years lost 78% of their spongy bone.

- **DELMAR PHARMA's VAL-083**, which is being investigated to treat glioblastoma multiforme and other tumors, was granted orphan drug status by the FDA.

- **GLAXOSMITHKLINE and ANACOR's GSK-2251052** – Anacor announced that GSK stopped two Phase II trials of this investigational antibiotic for urinary tract and intra-abdominal infections after it was found that disease-causing microorganisms might make the drug less effective.

- **IDENIX PHARMACEUTICALS' IDX-184** – After the company gave the FDA positive, new interim data last month from an ongoing 12-week Phase IIb trial in hepatitis C of this nucleotide polymerase inhibitor + pegylated interferon + ribavirin, the FDA lifted the partial clinical hold it had imposed due to safety concerns raised by a different combination study.

- **Metformin** – New guidelines published in the ***Annals of Internal Medicine*** advise that metformin should be the first choice for oral therapy of Type 2 diabetes, but only after diet and lifestyle changes have been tried. The guidelines call for a second agent to be added to metformin (not replace it) if metformin monotherapy is not sufficient, but the guidelines did not find sufficient evidence to recommend one secondary agent over another.

- **MINDCHILD MEDICAL's Meridian** – The company submitted a 510(k) application to the FDA for this non-invasive heart monitor to track the health of unborn babies.

- **NEUROGESX's Qutenza (transdermal capsaicin)** – The FDA's Anesthetic and Analgesic Drug Products Advisory Committee voted 12-0 that this pain patch did not relieve neuropathic pain from HIV, concluding the benefits do not outweigh the risks.

- **OCULAR THERAPEUTIX's ReSure Sealant**, a proprietary synthetic hydrogel polymer for ophthalmic use over clear corneal incisions, was granted an investigational device exemption (IDE) to conduct a pivotal 24-site clinical trial.
- **OREXIGEN THERAPEUTICS' Contrave (naltrexone + bupropion)** – The company reached agreement with the FDA on a special protocol assessment (SPA) for a 10,000-patient cardiac safety trial that the FDA wants for this diet drug.
- **Osteoporotic fractures** – A Canadian study published in the ***Journal of Clinical Endocrinology & Metabolism*** found that heart failure patients have a 28% increased risk of a major osteoporotic fracture, regardless of their bone mineral density (BMD). The retrospective database analysis of 45,509 individuals found the absolute increase in risk doubles with heart failure (from 5% to 10%).
- **PFIZER's Vantin (cefpodoxime)**, a cephalosporin antibiotic, was not very good at treating bladder infections in a 300-patient study published in the ***Journal of the American Medical Association***. The study tested two doses (100 mg BID and 250 mg BID) given for three consecutive days, but the researchers found it was not a viable alternative to the antibiotics currently used for bladder infections.
- **ROCHE/GENENTECH's pertuzumab** (formerly Omnitarg) was granted priority review by the FDA for use in combination with **Herceptin (trastuzumab)** and **docetaxel** in HER2+ metastatic or locally recurrent, unresectable breast cancer. The PDUFA date is June 8, 2012.
- **Rotavirus vaccine** – A large study published in the ***Journal of the American Medical Association*** found that the risk of intussusception was not increased at either 1 week or 1 month after administration in American babies who received the current pentavalent rotavirus vaccine (RV5) – **Merck's RotaTeq**.
- **SALIX PHARMACEUTICALS' crofelemer** for HIV-related diarrhea was granted priority review by the FDA. The PDUFA date is June 5, 2012.
- **SIEMENS** plans to work with **ViiV Healthcare** (which is developing an HIV drug) and **Tocagen** (which is developing a brain cancer drug) to create tests to determine which patients will benefit from the therapies.
- **SSRI antidepressants** – A review, published in the ***Archives of General Psychiatry***, of 41 clinical trials with a total of >9,000 adults and children found no reason to believe that antidepressants – well, at least not fluoxetine (**Lilly's Prozac**) or venlafaxine (**Pfizer's Effexor**) – influence suicidal thinking in children.
- **VIROPHARMA's Cinryze (C1 esterase inhibitor)** – The FDA rejected the company's plan to expand production of this drug to treat hereditary angioedema, issuing a complete response letter asking for validation of cleaning procedures for industrial-scale production.
- **WOUND MANAGEMENT TECHNOLOGIES** sold **Secure eHealth**, a non-core subsidiary, saying it intends to focus on **CellerateRX**, its collagen product.
- **ZIOPHARM ONCOLOGY's Zymafos (palifosfamide)** – The company said the FDA accepted its investigational new drug (IND) application for an oral version of this cancer drug. An IV version is in Phase III development in metastatic soft-tissue sarcoma.

NEWS IN BRIEF

CARDINAL HEALTH – in DEA's crosshairs

The Drug Enforcement Administration (DEA) raided two **CVS** pharmacies in the same general area in Florida, saying they were dispensing unusually high amounts of opioids. The pharmacies reportedly ordered >3 million oxycodone capsules last year, more than 20 times what the average pharmacy orders. The DEA tried to block shipments to the pharmacies from the company's Lakeland FL distribution center, but a judge stopped that.

The DEA suspended the pharmacies' license to prescribe controlled substances. The DEA also issued a suspension order against Cardinal Health for what it called "its alleged role in the state's prescription drug abuse problem." However, Cardinal convinced a judge to issue a temporary restraining order that allows the pharmacies to continue to dispense controlled drugs and delayed any action against Cardinal at least until a hearing is held in Washington DC this coming week.

EISAI

- **Dacogen (decitabine).** The FDA's Oncologic Drugs Advisory Committee (ODAC) voted 10-3 (with one abstention) against recommending a new indication – to treat acute myeloid leukemia (AML) in older patients – for this drug, which already is approved to treat myelodysplastic syndrome (MDS). The PDUFA date in AML is March 6, 2012.
- **Targretin (bexarotene).** A study published in the journal ***Science*** found that mice with early-stage Alzheimer's disease had some of their brain abnormalities reversed and their

declining mental function restored when they were given low doses of this cancer drug for cutaneous T-cell lymphoma. The drug quickly reduced amyloids in the brain – and, more important, mental function, memory, and smell improved.

MERCK

- **Victrelis (boceprevir).** The FDA warned doctors that giving this hepatitis C drug to HIV patients being treated with protease inhibitors – e.g., **Bristol-Myers Squibb's Reyataz** (atazanavir), **Johnson & Johnson's Prezista** (darunavir), or **Abbott's Kaletra** (lopinavir/ritonavir) – that are boosted with **Abbott's Norvir** (ritonavir) can reduce the effectiveness of the HIV drugs. The FDA said it will update the Victrelis label to include this drug interaction information.
- **Vorapaxar.** The company released top-line results from the TRA-2P trial of this PAR-1 thrombin receptor antagonist, which showed that vorapaxar significantly reduced the risk of a cardiovascular event but also significantly increased the risk of intracranial bleeding, though that risk was lower in patients without a prior history of stroke. The complete results of this 26,449-patient trial will be presented at the American College of Cardiology meeting in March 2012.

NEOVISTA's Vidion ANV brachytherapy – failed in AMD trial

The results of the Phase III CABERNET trial were finally presented at the Bascom Palmer Eye Institute's Angiogenesis, Exudation, and Degeneration 2012 meeting, and the trial missed its primary endpoint, failing to show a significant improvement in visual acuity at two years with this epimacular beta radiation 24 Gy therapy for wet age-related macular degeneration (AMD). In the 457-patient, prospective multicenter, randomized trial, the radiation was given in conjunction with **Roche/Genentech's Lucentis** (ranibizumab).

The failure could have been due to trial design, patient selection, probe placement, unusually good results in control patients, or just an ineffective therapy.

There is still another radiation therapy for AMD in development, **Oraya's IRay**, and if its INTREPID trial fails – the results are expected this summer – it may be the nail in the coffin for brachytherapy of the eye. But Oraya officials are still optimistic that their trial will be successful. IRay differs from Vidion in several key ways, including: It's non-invasive, with precise, robotic positioning and a lower dose, and its trial is sham-controlled and double-blind.

NOVARTIS' Bexsero, a meningococcal B vaccine – positive data

A 1,885-infant study published in the ***Journal of the American Medical Association*** reported that the vaccine protected infants against disease when given together with routine childhood inoculations, suggesting it could be included in standard vaccination programs. In an accompanying editorial, two researchers from the Centers for Disease Control and Prevention (CDC) called the results "a major step forward."

PFIZER's Aromasin (exemestane) – causes bone loss

A study published in ***Lancet Oncology*** found that this aromatase inhibitor, used to prevent breast cancer recurrence, appears to cause significant bone loss. Now, the question is whether the 65% reduction in breast cancer recurrence is offset by the increased risk of fractures. The MAP-3 substudy used CT scans to get a detailed look at the women's bones.

After two years on the study, BMD dropped at the spine, hip, neck, and elsewhere, even with calcium and vitamin D supplementation. For example, wrist BMD dropped 6.1% vs. 1.8% with placebo. In an accompanying editorial, Jane Cauley, DrPH, an epidemiologist at the University of Pittsburgh, said the study suggests that the negative side effects of aromatase inhibitors on bone are "substantially underestimated."

Proton pump inhibitors (PPIs) – linked to *C. diff*

The FDA issued a Drug Safety Communication warning of a possible link between PPIs and *Clostridium difficile*-associated diarrhea (CDAD). All of the PPIs are affected, not just one or some. The FDA warned that a diagnosis of CDAD should be considered for patients taking PPIs who develop diarrhea that does not improve, and patients should use the lowest dose possible for the shortest possible duration. Label changes are coming for PPIs. And the FDA also is investigating whether the same problem occurs with histamine H2 receptor blockers used to treat gastroesophageal reflux disease (GERD), etc.

ROCHE/GENENTECH's Activase (alteplase, tPA) – new scoring system to predict outcomes

A new scoring method, the 10-point DRAGON score, has been developed to help identify which ischemic stroke patients will respond well to this clot-busting drug. In a 1,319-patient study reported in ***Neurology***, the medical journal of the American Academy of Neurology, DRAGON was found to be 86% accurate in predicting the outcome three months post-stroke in patients who received the drug within the 4.5-hour efficacy window.

The researchers said the DRAGON score is simple and fast to perform and is free. The higher a patient's score, the more likely a bad outcome. In the study, 96% of patients with a DRAGON score of 0-2 had a good 3-month outcome vs. none of the patients with a DRAGON score of 8-10.

REGULATORY NEWS

FDA issues draft guidance for biosimilar drugs

The FDA issued three draft guidance documents on biosimilar product development to assist development of these products in the U.S. The FDA defines a biosimilar as "a biological product that is highly similar to an already approved biological product, notwithstanding minor differences in clinically inactive components, and for which there are no clinically meaningful differences between the biosimilar and the approved biological product in terms of the safety, purity, and potency."

Among the key points in the new FDA guidance:

- Biosimilars will be reviewed as a package, with the FDA considering the totality of the evidence.
- The FDA is taking a stepwise approach.
- "Biosimilar" does not mean "identical."
- Biosimilarity and interchangeability are sequential decisions. They can be done in the same 10-month approval period only if that is requested *initially*. If interchangeability is requested later in the approval process, it extends the approval period.
- Interchangeability will require a switching study.
- The reference product has to be FDA-approved; European approval is not sufficient.

For more details, see ***Trends-in-Medicine*** *Bulletin on Biosimilars.*

Medical device tracking system delay

Why isn't there already a standardized coding system – the Unique Device Identifier (UDI) – to track medical devices? The Office of Management and Budget (OMB) is the bottleneck. In 2007 Congress directed the FDA to create a medical device coding system using scanning technology so devices like pacemakers, hip implants, stents, and breast implants, etc., could be tracked. It took the FDA a while, but last summer, the FDA sent its proposed regulations to the Office of Management and Budget, which has to give its approval.

However, it is as if the proposed rule dropped into a black hole. Everyone is still waiting for OMB to act, and OMB is not saying when it will do that. Three senators – Herb Kohl (D-WI), Richard Blumenthal (D-CT), and Charles Grassley (R-IA) – wrote OMB demanding an explanation for the delay in releasing the proposed rule on UDI.

NIH boosts Alzheimer's disease funding

The National Institutes of Health plans to budget an additional $50 million for dementia research, and President Obama plans to ask Congress for another $80 million for 2013. This is all part of the administration's National Alzheimer's Plan, which aims to find an effective treatment by 2025.

Possible repeal of medical device excise tax?

Seventy-five legislators wrote to the House Republican leadership, calling for a vote Monday, February 13, 2012, on the floor of the House on the Protect Medical Innovation Act of 2011, which would repeal the 2.3% medical device excise tax, which they called "onerous and irresponsible."

FDA approvals/clearances

- **CASE MEDICAL's MediTray products and SteriTite container system** were given 510(k) clearance for use in the company's sterilizers.
- **EDEN SPINE's GIZA**, a device used to replace and fuse an unstable vertebral body due to fracture or tumor, was granted 510(k) clearance.
- **MOBIUS THERAPEUTICS' Mitosol (mitomycin)** – The FDA approved this glaucoma surgery drug.
- **ST. JUDE MEDICAL's Safire Blu Duo and Therapy Cool Path Duo catheters** were granted PMA approval to treat patients with atrial flutter.
- **SHIRE's Vyvanse (lisdexamfetamine)** – The FDA approved expanded uses of this attention-deficit/hyperactivity disorder drug for use in adults, not just children.

FDA recalls/warnings

- **BIOMEDICA DIAGNOSTICS**, which manufactures plasma/coagulation control products, received a 483 Letter from the FDA that its manufacturing standards were deficient.
- **CADENCE PHARMACEUTICALS' Ofirmev (IV acetaminophen)** – The company voluntarily recalled one lot of this pain medication after finding an unidentified particulate matter in a vial during routine drug-stability testing.

- **MERIT MEDICAL SYSTEMS** received an FDA warning letter for failing to notify the FDA about a change in the manufacturing of its diagnostic and catheter guidewires.
- **NEWMAN LASIK CENTERS** of Hercules CA was notified by the FDA that it did not meet the Agency's standards for developing, maintaining, and implementing written Medical Device Reporting (MDR) procedures – it wasn't reporting LASIK adverse events properly.
- **PHOTOMEDEX** received a warning letter from the FDA that cited quality violations and misbranding of some of its wound dressing products.

European regulatory actions

BOSTON SCIENTIFIC's Infinion 16 percutaneous lead was granted a CE Mark for use in conjunction with the company's Precision Plus spinal cord stimulator for managing chronic pain.

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

ROCHE's RoActemra (tocilizumab) – This anti-IL6 therapy was approved to treat systemic juvenile idiopathic arthritis.

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
	February 2012	
February 15	Reauthorization of **FDA user fee program for medical devices**	Health subcommittee of House Energy and Commerce Committee hearing
February 17	**Corcept Therapeutics' Corlux** (mifepristone) for Cushing's syndrome	PDUFA date
February 22	**Vivus' Qnexa** (phentermine + topiramate), a diet drug	FDA's Endocrinologic and Metabolic Drugs Advisory Committee
February 23	**Chelsea Therapeutics' Northera** (droxidopa) for symptomatic neurogenic orthostatic hypotension with primary autonomic failure	FDA's Cardiovascular and Renal Drugs Advisory Committee
February 23	**Forest Laboratories' Eklira** (aclidinium bromide) for chronic obstructive pulmonary disease (COPD)	FDA's Pulmonary-Allergy Drugs Advisory Committee
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 28-29	Flu vaccine update, including **Pandemic Influenza Surveillance** and licensure pathways for pandemic flu vaccines	FDA's Vaccines and Related Biological Products Advisory Committee
	March 2012	
March 3	CMS National Coverage Decision on **TAVR** ends	CMS public comment period ends
March 6	**Discovery Labs' Surfaxin** (lucinactant) for infant respiratory disease	PDUFA date
March 6	**Eisai's Dacogen** (decitabine) to treat acute myeloid leukemia (AML) in older patients	PDUFA date
March 7	**NeurogesX's Qutenza** (transdermal capsaicin) for neuropathic pain	PDUFA date
March 12	Safety of **anti-nerve growth factor (anti-NGF) drugs** in development to treat a variety of pain conditions. The questions are: Do reports of joint destruction represent a safety signal, and does the risk:benefit balance favor continued development?	FDA's Arthritis Advisory Committee
March 20	**GlaxoSmithKline's Votrient** (pazopanib) for advanced soft-tissue sarcoma (in the morning), and **Merck/Ariad's Taltorvic** (ridaforolimus) for maintenance therapy of metastatic soft-tissue sarcoma or bone sarcoma (in the afternoon)	FDA's Oncologic Drugs Advisory Committee (ODAC)
March 21	**Talon Therapeutics' Marqibo** (vincristine sulfate liposomes injection) for Philadelphia chromosome-negative acute lymphoblastic leukemia (ALL)	FDA's Oncologic Drugs Advisory Committee (ODAC)
March 26	**MAP Pharmaceuticals' Levadex** (dihydroergotamine inhalation) for migraine	PDUFA date
March 26-27-28	Oral arguments on the **legality of Obamacare**	U.S. Supreme Court
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 ***– delayed but new date not available. FDA panel is May 23.***
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
March 28-29	Two-day discussion of pre-and post-approval assessment of **cardiovascular safety for diet drugs and biologics**	FDA's Endocrinologic and Metabolic Drugs Advisory Committee
	April 2012	
April 5	**Astellas' mirabegron**, a beta-3-adrenoceptor agonist to treat overactive bladder (OAB)	FDA's Reproductive Health Drugs Advisory Committee
April 17	**Vivus' Qnexa** (phentermine + topiramate) for weight loss	PDUFA date for resubmission
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 castration-resistant 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
2Q12	**Arena Pharmaceutical and Eisai's Lorqess** (lorcaserin) for weight loss	FDA's Endocrinologic and Metabolic Drugs Advisory Committee

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	PDUFA date
May 4	**Alexza Pharmaceuticals' Adasuve** (loxapine inhalation powder) for the acute treatment of agitation associated with schizophrenia/bipolar I disorder	PDUFA date
May 13	**Talon Therapeutics' Marqibo** (vincristine sulfate liposomes injection) for Philadelphia chromosome-negative acute lymphoblastic leukemia (ALL)	PDUFA date
May 23	**Bristol-Myers Squibb's Eliquis** (apixaban), an anticoagulant for prevention of stroke in AFib	FDA's Cardiovascular and Renal Drugs Advisory Committee
June	**Forest Laboratories and Ironwood Pharmaceuticals' linaclotide** for IBS-C	PDUFA date
June 5	**Salix Pharmaceuticals' crofelemer** for HIV-related diarrhea	PDUFA date
June 8	**Roche/Genentech's pertuzumab** in HER2+ advanced breast cancer	PDUFA date
June 25	**QRxPharma's MoxDuo** (morphine + oxycodone)	PDUFA date
June 26	**Edwards Lifesciences' Sapien** transcatheter aortic valve	CMS final NCD expected
June 29	**Astellas Pharma's mirabegron** for treatment of overactive bladder	PDUFA date
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 27	**Onyx Pharmaceuticals' carfilzomib** for multiple myeloma	PDUFA date
July 30	**Regeneron's Arcalyst** (rilonacept) for gout	PDUFA date
August 21	**Pfizer's tofacitinib**, an oral JAK2 inhibitor for rheumatoid arthritis	PDUFA date
August 27	**Gilead Sciences' Quad** (emtricitabine + tenofovir + elvitegravir + cobicistat) for HIV	PDUFA date