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

- **ADVANCED CELL TECHNOLOGY** received clearance from the U.K.'s Medicines and Healthcare Products Regulatory Agency (MHRA) to begin treating patients as part of a Phase I/II trial in Stargardt's Macular Dystrophy using retinal pigment epithelium (RPE) derived from human embryonic stem cells. The company also received approval from the Gene Therapy Advisory Committee (GTAC) and already had been granted orphan drug status by the European Medicines Agency (EMA).

- **AMGEN's Prolia (denosumab)** was given an expanded indication to prevent bone fractures in patients with breast or prostate cancer who are undergoing hormone therapy. It was originally approved for postmenopausal women at high risk of osteoporotic fracture.

- **Biosimilars** – One of the ways President Obama hopes to reduce the deficit is by encouraging biosimilars, and to do that, his plan is to reduce exclusivity of brand biologics from 12 years to 7.

- **GILEAD SCIENCES' Quad (tenofovir + emtricitabine + elvitegravir + cobicistat)** – The company announced this four-drug cocktail was equivalent, but not superior, to a combination of three approved drugs – **Gilead's Truvada** (tenofovir + emtricitabine) + **Bristol-Myers Squibb's Reyataz** (atazanavir) + **ritonavir** – in treating HIV. Efficacy was 90% with the Quad vs. 87% with the 3-drug combination. Gilead plans to file the Quad with the FDA by the end of 2011.

- **HOSPIRA's Retacrit (biosimilar Epogen)** – Hospira announced it plans to begin a Phase III trial in the U.S. by the end of 2011 of this biosimilar to **Amgen's Epogen** (epoetin alfa) in renal dysfunction patients with anemia. ***The New York Times*** reported Hospira CEO Michael Ball said, "Biosimilars are not miracle drugs…They are real. We are really selling them in Europe, we're really selling them in Australia, and we will be selling them here in the United States."

- **IMMUNOGEN's IMGN-529** – The company submitted an application to the FDA to study this in cancer, including non-Hodgkin's lymphoma and chronic lymphocytic leukemia (CLL).

- **IMMUNOMEDICS' clivatuzumab tetraxetan** – The FDA stopped a study of this pancreatic cancer drug after one patient received an incorrect dose. The patient reportedly was unharmed and is still in the trial. The company said it is working with the FDA to file the necessary paperwork to resume the trial.

- **IRIDEX** licensed the exclusive rights to all of the intellectual property of **Ocunetics**.

- **JAZZ PHARMACEUTICALS** is buying privately held **Azur Pharma**, which sells 10 drugs in the U.S., including schizophrenia drugs, drugs for women's health disorders, and **Prialt** (ziconotide) for severe chronic pain.
- **JOHNSON & JOHNSON's Tylenol** – J&J resumed shipping Tylenol Cold & Flu Severe caplets after a long series of recalls, but the company wouldn't confirm reports that the new product is being manufactured in Italy.
- **MERCK KGAA** acquired worldwide exclusive rights to **Peptimmune's PI-2301**, a drug for multiple sclerosis.
- **NUVASIVE** lost a patent infringement lawsuit brought by **Medtronic** and was ordered to pay $101.2 million in damages. The court found three NuVasive spinal products – CoRoent XL implants, MaXcess II and III retractors, and Helix and Helix mini anterior cervical plates – violate Medtronic patents.
- **OPTOS** is buying the ophthalmic instrumentation business of **Opko Health**.
- **QLT's QLT-091001**, a drug to treat two degenerative eye diseases – Leber congenital amaurosis (LCA) and retinitis pigmentosa (RP) – was granted fast track status by the FDA. It already has orphan drug status.
- **SHIRE's ProAmatine (midodrine)** – Shire requested a public hearing over the FDA's postmarketing requirement for this blood pressure medicine. ProAmatine was approved in 1996, but the FDA required Shire to conduct follow-up efficacy studies. Shire hopes a public hearing will convince the FDA to give final approval without additional trials.
- **SUN PHARMACEUTICAL INDUSTRIES** has resolved the issues raised by the FDA in an August 2010 warning letter about manufacturing violations at its New Jersey plant.
- **Sunscreen research** – The National Institutes of Health gave a $454,000 three-year grant to chemist Martha Hass of Albany College of Pharmacy and Health Sciences for her research into a substance created in her lab that may mitigate ultraviolet skin damage. The substance is a combination of two antioxidants – vitamin E and lipoic acid – into a more potent single molecule. There's no company involved yet, but there will be.
- **TOPCON and LENSAR** have formed a strategic partnership under which Topcon will be responsible for the distribution and marketing in Europe of LensAR's LensAR Laser System for anterior capsulotomy and lens fragmentation during cataract surgery, which was granted FDA 510(k) clearance in March 2011.
- **VALEANT PHARMACEUTICALS** – The Federal Trade Commission (FTC) wants more information on Valeant's proposed takeover of the dermatology units of **Sanofi** and **Janssen Pharmaceuticals**.
- **VARIAN MEDICAL SYSTEMS** is acquiring **Calypso Medical Technologies**, gaining products for tracking tumor motion during radiosurgery and radiotherapy.
- **VIIV HEALTHCARE's Selzentry (maraviroc)** – The company withdrew its applications to the FDA and European regulators for this once-daily HIV drug, saying additional data are necessary to establish the efficacy of QD dosing.
- **WRIGHT MEDICAL** agreed to a one-year extension (until September 29, 2012) of its deferred prosecution deal with New Jersey prosecutors after the prosecutors charged Wright had not met the terms of the original deal.

NEWS IN BRIEF

ALEXION PHARMACEUTICALS' Soliris (eculizumab) – new indication

This orphan drug got accelerated approval for a new indication – to treat patients with atypical Hemolytic Uremic Syndrome (aHUS), a rare and chronic blood disease that can lead to renal failure, death, and stroke. This is the first FDA-approved treatment for aHUS. Soliris was already approved to treat paroxysmal nocturnal hemoglobinuria (PNH), another rare blood disorder.

The aHUS approval comes with a Risk Evaluation and Mitigation Strategy (REMS) that requires the company to inform healthcare professionals and patients about the known risk of life-threatening meningococcal infections. Soliris will only be available through a restricted access program, and doctors must enroll in a registration program and give patients a medication guide.

Atypical antipsychotics – concerns about pediatric use continue

The FDA's Pediatric Advisory Committee voted 16-1 that the Agency should continue to monitor the safety and side effects of atypical antipsychotics in children. The panel also recommended the FDA re-label the drugs to emphasize increased risks for diabetes and weight gain in children. And the panel voted 17-0 to require the FDA to share proposed new labels with the panel and to check back within the next 12-18 months on the progress in designing additional studies of these medications in children.

BOEHRINGER INGELHEIM's BIBF-1120 – promising in IPF but not a home run

In an international, 432-patient, 1-year Phase II trial in idiopathic pulmonary fibrosis (IPF), published in the ***New England Journal of Medicine***, this oral tyrosine kinase inhibitor missed the primary endpoint, failing to show a significant decrease in the annual rate of decline in forced vital capacity (FVC).

However, the researchers still believe the drug is a promising treatment for IPF because the BIBF-1120 patients had significantly fewer acute exacerbations and a trend toward slower decline in lung function. The rate of progression declined almost 70% in patients on the highest of the four doses tested (150 mg BID) vs. placebo, and acute exacerbations occurred 84% less frequently. Quality of life also improved with BIBF-1120. Yet, none of the BIBF-1120 doses significantly reduced the rate of disease progression (p=0.06 for 150 mg).

While GI toxicity was more frequent with the 150 mg dose, the incidence of serious adverse events was no different from placebo.

BRISTOL-MYERS SQUIBB

- Is buying the rights to two preclinical **Ambrx** drugs – **Fibroblast Growth Factor 21** (FGF-21) for diabetes and **Relaxin** (methocarbamol) for heart failure – and plans to collaborate on their research and development.
- Granted marketing rights in Japan to its rheumatoid arthritis drug **Orencia** (abatacept) to **Ono Pharmaceutical** in exchange for world marketing rights outside Japan, Korea, and Taiwan, for the anti-PD-1 antibody BMS-936558/ ONO-4538 that is in Phase I/II development to treat cancer, particularly renal cell carcinoma and melanoma.

European Multidisciplinary Cancer Congress news

- **AMGEN's Xgeva (denosumab)** – A 1,432-patient study by French researchers found Xgeva delayed the onset of bone metastases by ~4 months in castration-resistant prostate cancer (CRPC).
- **BAYER's Alpharadin (radium-223 chloride)** – The Phase III ALSYMPCA trial of this alpha-pharmaceutical showed significantly improved survival in advanced prostate cancer patients with bone metastases vs. best standard therapy.
- **JOHNSON & JOHNSON's Zytiga (abiraterone)** – A study found men with CRPC suffered from less fatigue when treated with abiraterone + prednisone. Previously, it was shown to have a survival benefit, but this study showed it also improves quality of life.
- **NOVARTIS**
  - **Femara (letrozole)** – The 12-year results of the BIG 1-98 trial found this aromatase inhibitor continues to prevent breast cancer recurrences and reduces the risk of death in postmenopausal women with hormone receptor-positive early breast cancer better than tamoxifen.
  - **Zometa (zoledronic acid)** – The AZURE trial found this IV bisphosphonate reduced the recurrence of breast cancer in postmenopausal women by 25%. Overall survival was 85% vs. 79% for women who did not get Zometa.
- **ROCHE**
  - **Avastin (bevacizumab)** – A combination of Avastin and **pemetrexed (Lilly's Alimta)** increased progression-free survival by 3.6 months in previously untreated non-squamous non-small cell lung cancer in the Phase III AVAPERL trial (10.2 months vs. 6.6 months with Avastin alone, HR=0.50; p<0.001). No new adverse events were observed with the combination.
  - **Boniva (ibandronate)** – A 470-patient Phase III U.K. trial found a single infusion of this bisphosphonate was just as good for pain relief in prostate cancer that has metastasized to the bone as single-dose radiotherapy, the standard therapy.
  - **Trastuzumab emtansine (T-DM1)** – A randomized Phase II study showed this antibody-drug conjugate significantly improved progression in HER2+ breast cancer by 41% vs. standard docetaxel + Herceptin (trastuzumab).

Lasers – comparable to standard varicose vein therapy

Laser ablation for varicose veins was just as effective as conventional therapy in the 185-patient RELACS trial. The results, published in the ***Archives of Dermatology***, showed similar two-year recurrence rates for endovenous laser treatment (EVLT) and high ligation with stripping (HLS) – 16.2% vs. 23.1%. However, researchers also found saphenofemoral reflux occurred significantly more often after EVLT (17.8% vs. 1.3%, p<0.001). They concluded that EVLT and HLS are equally effective and safe in treating great saphenous vein insufficiency, with "minor" advantages for EVLT in terms of patient satisfaction with cosmetics and convalescence.

OREXIGEN THERAPEUTICS and TAKEDA's Contrave (bupropion + naltrexone) – the story's not over

The company has decided not to give up on this diet drug after all. In June 2011, Orexigen said it was giving up on Contrave because of the FDA's "unprecedented" approval requirements. However, after meeting with the FDA, the company has decided to begin a 10,000-patient cardiovascular safety trial in 2012. The company said the Agency told it that the drug could be approved by 2014 if an interim analysis excludes "an unacceptable increased cardiovascular risk."

ORION PHARMA's Simdax (levosimendan) – possible new role in respiratory illnesses

This calcium sensitizer, which is approved to treat heart failure, also may be effective in improving muscle function in patients with respiratory failure by improving the function of the diaphragm. In a 30-patient study published in the American Thoracic Society's ***American Journal of Respiratory and Critical Care Medicine***, Dutch researchers reported healthy volunteers given the drug had improved muscle contractility, suggesting it may help in conditions like chronic obstructive pulmonary disease (COPD) and congestive heart failure (CHF).

Patients on placebo lost 9% of their muscle contraction following exercises, but the levosimendan patients had no loss of contraction. In addition, the mechanical efficiency of the diaphragm during the exercises improved by 21% with levosimendan vs. placebo, which meant the levosimendan subjects needed less effort than placebo subjects to achieve the same amount of muscle force in the diaphragm.

PFIZER's Tygacil (tigecycline) – FDA finds explanation for safety question

The slight increase in mortality that caused the FDA to change the label last year for this IV antibiotic is more likely related to lack of efficacy than to toxicity, a detailed FDA analysis presented at the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) concluded. FDA reviewers found 44.2% of the Tygacil deaths due to lack of efficacy, compared to 39% of deaths with agents. Toxicity was ruled the likely cause of death in 6.1% of Tygacil patients vs. 3.8% of deaths with other agents.

Platelet function testing – study finds it a poor prognostic sign

The results of the RECLOSE 2-ACS trial, using platelet testing by light transmittance aggregometry, were published in the ***Journal of the American Medical Association*** (JAMA). The primary endpoint in this Italian study of 1,789 PCI patients on clopidogrel – a composite of cardiac death, MI, urgent revascularization, and stroke at two years – was significantly higher in patients with high residual platelet reactivity (HRPR) vs. patients with low residual platelet reactivity (14.6% vs. 8.7%, p=0.003). Stent thrombosis was also significantly higher in the HRPR patients (6.1% vs. 2.9%, p=0.01).

In an accompanying editorial, Dominick Angiolillo, MD, PhD, from the University of Florida College of Medicine-Jacksonville said routine platelet function testing to adjust the dosing of clopidogrel is not justified in clinical practice. Instead, he said the tests should be reserved for research.

ROCHE

- **No pay, no drugs.** Roche cut off delivery of prescription drugs – particularly cancer and chronic disease drugs – to some nationally funded hospitals in Greece, saying the hospitals haven't paid their bills in three or four years. However, Roche increased deliveries to hospitals that have a consistently good payment record. Roche is considering similar measures for government-funded hospitals that haven't been paying in a timely manner in Italy, Portugal, and Spain. *Watch for other pharmas to follow suit.*
- **Roche/Genentech's Avastin (bevacizumab).** The Department of Veterans Affairs said it will stop off-label ophthalmic use of this ~$50/injection drug to treat wet age-related macular degeneration while it investigates reports of serious infections and blindness. *While this will be a temporary boost for Roche/Genentech's expensive (~$2,000/injection)* ***Lucentis*** *(ranibizumab), the big winner may be* ***Regeneron's aflibercept*** *if it is approved by the FDA and if it is cheaper.*
- **Xenical (orlistat) and GlaxoSmithKline's Alli (over-the-counter orlistat).** The EMA is reviewing the risk:benefit of these diet drugs after 21 reports of severe liver injury. While liver damage was a known adverse event, these cases were serious enough to prompt the review. A 2009 European review of orlistat and serious hepatic reactions found insufficient evidence of causality, but the issue is being revisited.

REGULATORY NEWS

Congress eyes cutting some Medicare extra payments

The Centers for Medicare and Medicaid Services (CMS) pays ~$2.3 billion a year for "extra" payments – things like geographic payment adjustments for doctors who practice in expensive areas, ambulance services, certain mental health

services, and outpatient therapy (speech, physical, and occupational). The Health Subcommittee of the House Ways and Means Committee is reviewing these payments, many of which have been extended repeatedly, to see if they can find some areas they can refuse to renew when they expire on January 1, 2012.

FDA gets tougher on unapproved drugs

Changing the formulation of an unapproved drug to avoid FDA regulatory action is likely to backfire on companies. The FDA announced companies marketing unapproved drugs that change the formulation to evade attention are high on the Agency's enforcement list. The FDA issued revised guidance on unapproved drugs, warning, "All unapproved drugs introduced onto the market after [September 19, 2011] are subject to immediate enforcement action at any time, without prior notice."

FDA's 510(k) reform

Jeffrey Shuren, MD, director of the Center for Devices and Radiologic Health (CDRH), said the FDA may be close to a decision on the 510(k) reforms, with an announcement perhaps by the end of October 2011.

European regulatory actions

- **COHERA MEDICAL's TissuGlu**, a surgical adhesive, was approved. The company plans to file for FDA approval by the end of 2011 and start clinical trials early in 2012.
- **ROCHE's Avastin (bevacizumab)** received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) for the use in combination with standard chemotherapy (carboplatin and paclitaxel) as a front-line treatment for women with advanced ovarian cancer.
- **SANOFI's Multaq (dronedarone)** – European regulators plan to restrict the use of this atrial fibrillation drug (an alternative to amiodarone) because of liver, lung, and cardiovascular safety issues, restricting use to patients with a persistent, paroxysmal irregular heartbeat, and then only after alternative treatments have been tried.
- **UCB PHARMA's Vimpat (lacosamide 15 mg/ml syrup)** – In August the EMA recalled this antiepileptic medication because a quality issue in some batches resulted in an uneven distribution of the active substance in the syrup. Now, the CHMP has recommended the product be removed from the market permanently.
- **VERTEX PHARMACEUTICALS and JOHNSON & JOHNSON's Incivo (telaprevir)**, a direct-acting protease inhibitor to treat hepatitis C, was approved in combination with peginterferon-alfa and ribavirin.

FDA approvals/clearances

- **MAQUET CARDIOVASCULAR's Sensation Plus 50cc 8 French intra-aortic balloon catheter** was cleared by the FDA. It also was granted a CE Mark.
- **MEDX HEALTH's MoleMate**, a skin imaging tool that helps doctors examine lesions and suspicious moles, was cleared for use.
- **VERAX BIOMEDICAL's Platelet PGD test** for bacterial contamination in platelets prior to transfusion was cleared for use. It already had a CE Mark.

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

- **ASTRAZENECA's Brilinta/Brilique (ticagrelor)** – The final guidance on use of this antiplatelet agent endorses its use in combination with aspirin for up to 12 months in adults with acute coronary syndrome.
- **JOHNSON & JOHNSON's Zytiga (abiraterone)** is still being reviewed for cost-effectiveness – given a price of £3,000/month (USD $4,700) – even though NICE concedes it extends survival by ~4 months.

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
	September 2011	
September 26	**Drug shortages**	FDA public workshop
September 26-27	**Tissue adhesive materials**	FDA workshop on facilitating innovation in these products
September 30	Institute of Medicine's recommendations for FDA's reform of the **510(k) device clearance program**	Public comment deadline
	October 2011	
October 12	**FDA guidance on diagnostic tests** being developed simultaneously with a drug/biologic	New deadline for industry comment
October 13	**Cook's Zilver-PTX** paclitaxel-eluting, non-polymer stent	FDA's Circulatory System Devices Advisory Committee
October 13	**Highly multiplexed microbiology/medical countermeasure (MCM) devices,** for identifying potential disease etiology	FDA public meeting
October 14	**GenProbe's Progensa PCA3 assay** to aid in the decision for repeat biopsyin men age ≥50 with ≥1 previous negative prostate biopsy	FDA's Immunology Devices Advisory Committee - postponed
October 17	**Teva Neuroscience's Azilect** (rasagiline mesylate) for a new indication in Parkinson's disease	FDA's Peripheral and Central Nervous System Drugs Advisory Committee
October 25-26	**MRI safety and risk mitigation**	FDA public workshop
October 26	**AtriCure's AtriCure Synergy Ablation System** for radiofrequency atrial fibrillation	FDA's Circulatory System Devices Advisory Committee
October 27	**Medtronic's Ablation Frontiers Cardiac Ablation System** for atrial fibrillation via electrodes	FDA's Circulatory System Devices Advisory Committee
October 28	**Bristol-Myers Squibb** and **AstraZeneca's dapagliflozin,** the first SGLT-2 for Type 2 diabetes	PDUFA date
October 28	**Pacira Pharmaceuticals' Exparel** (bupivacaine ER), a painkiller	PDUFA date
	November 2011	
November 2	Discussion of regulatory, academic, and industry perspectives on the development of **anticoagulant products in children**	FDA's Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee (ODAC)
November 2	**Merck's Vytorin** (ezetimibe/simvastatin) and **Zetia** (ezetimibe), supplemental NDA to reduce major cardiovascular events in patients with chronic kidney disease (CKD), based on the results of the SHARP trial	FDA's Endocrinologic and Metabolic Drugs Advisory Committee
November 5	**Johnson & Johnson's Xarelto** (rivaroxaban) for stroke prevention in AFib	PDUFA date
November 16	**Pneumococcal 13v vaccine** safety and immunogencity in adults >age 50	FDA's Vaccines and Related Biological Products Advisory Committee
November 18	**Regeneron's Eylea** (aflibercept, VEGF Trap-Eye) for wet AMD	New PDUFA date
	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 8	**Antares Pharma's Anturol** (transdermal oxybutynin ATD gel), for overactive bladder	PDUFA date
December 13	**Endo Pharmaceuticals' Opana** (extended-release oxymorphone), a painkiller	PDUFA date
	Other 2011 events of interest	
4Q11	**Ophthotech's ARC-1905** primary endpoint results in Phase I trial in dry AMD	Company announcement or medical conference presentation
4Q11	**Roche/Genentech's Lucentis** (ranibizumab) – Phase III HARBOR trial one-year data on the 2 mg dose in wet AMD	Company announcement or medical conference presentation

2012 FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
January	**Pfizer's Prevnar 13** (PCV13), a pneumococcal vaccine for adults	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	**Alcon's tandospirone** for dry AMD – Phase III final data expected	Company announcement or medical conference presentation
February 17	**Corcept Therapeutics' Corlux** (mifepristone) for Cushing's syndrome	PDUFA date
February 28	**Pfizer's axitinib** for advanced renal cell carcinoma	PDUFA date (*approximate*)
March 27	**Affymax and Takeda's peginesatide** for anemia	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