TRENDS-in-MEDICINE

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Quick Takes

…Highlights from this week's news affecting drugs and devices in development…

SHORT TAKES

- **ALKERMES' ALKS-33**, a potential treatment for cocaine addiction, was well tolerated in combination with buprenorphine, an approved treatment, meeting Phase I safety goals. A Phase II trial is expected to begin in 1H11.
- **AMGEN's Prolia (denosumab) –** The U.K.'s National Institute for Health and Clinical Excellence (NICE) approved coverage of Prolia for post-menopausal women with osteoporosis.
- **ARIAD PHARMACEUTICALS' ridaforolimus –** Phase II results were positive, improving progression-free survival in 114 patients with endometrial or uterine cancer. PFS was 3.6 months with ridaforolimus vs. 1.9 months with standard treatment, a 1.7 month improvement. However, ~25% of ridaforolimus patients had serious side effects vs. 4% with standard treatment.
- **BIOSENSORS INTERNATIONAL** acquired the assets of **Devax**, including the Axxess drug-eluting stent (DES) for bifurcated lesions.
- **BOSTON SCIENTIFIC** sold its neurovascular, not its neuromodulation, business to **Stryker**.
- **BRISTOL-MYERS SQUIBB's belatacept –** The FDA said problems at the company's plant in Puerto Rico have to be resolved before belatacept, a selective co-stimulation (CTLA-4) blocker to prevent kidney transplant rejection, can be approved.
- **Coupons –** Use of coupons, vouchers, and discount cards to reduce or eliminate the copay for prescription drugs has risen 258% since 2006, according to IMS Health data.
- **FOREST LABORATORIES' Teflaro (ceftaroline fosamil)**, an injectable cephalosporin antibiotic, was approved by the FDA to treat adults with community-acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure infections (ABSSSI), including methicillin-resistant *Staphylococcus aureus* (MRSA).
- **GE Healthcare** was sued by 12 patients in Alabama who claimed they suffered symptoms such as hair loss and changes in cognition due to exposure to excessive radiation from GE's CT scanners.
- **GENZYME's Fabrazyme (agalsidase beta) –** The European Medicines Agency (EMA) said full dosing of Fabry disease patients should be resumed because patients receiving a smaller dose reported side effects. The EMA said it "remains concerned

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about a shortage of Fabrazyme after disruptions at Genzyme's Allston Landing factory in Boston," noting that Fabry patients "also can be given a full dose of Shire's Replagal (agalsidase alfa)."

- **GREENWAY MEDICAL TECHNOLOGIES** has acquired imaging technology and other assets from VisualMED, an imaging conversion and communications firm. The technology provides key imaging features for Greenway's PrimeImage, a PACS imaging system, enabling users of Greenway's electronic health record (EHR) product, PrimeSuite 2011, to integrate digital images into patient charts.

- **INFINITY PHARMACEUTICALS' IPI-940 – Purdue Pharmaceutical Products** and **Mundipharma International** are assuming worldwide development and commercialization activities for this oral fatty acid amide hydrolase (FAAH) inhibitor – an analgesic and pain reliever – after a 48-patient, single-dose Phase I study showed favorable pharmacokinetics and good toleration in healthy volunteers. Purdue is planning to start a Phase II trial in 2011.

- **INTELLECT NEUROSCIENCES' Oxigon (OX1) –** Preliminary data from a randomized, placebo-controlled, multiple escalating dose Phase 1b trial showed that this Alzheimer's disease therapy – which has antioxidant activity and presents deposition of amyloid beta – was safe and well tolerated in 12 healthy elderly volunteers during 14 days.

- **MACROGENICS** signed a global research collaboration and license deal with **Pfizer** to develop potential cancer treatments, focusing on MacroGenics' Dual-Affinity Re-Targeting products.

- **Medical device industry –** Canada and Australia have adopted an agreement under which they acknowledge each other's quality management system (QMS) certificates. This means that medical device manufacturers in those countries will no longer have to undergo duplicate evaluations. The agreement also applies to device firms in New Zealand.

- **MYREXIS (formerly Myriad Pharmaceuticals)** signed a deal with **Abbott Laboratories** for use of its technology to identify mutations in breast cancer patients enrolled in a Phase III study on a potential breast cancer treatment.

- **NOVARTIS's Xolair (omalizumab) –** The U.K.'s NICE rejected coverage of Xolair for severe asthma in children aged 6-11, saying it offered "limited" benefits compared to other available therapies and is not "good value for money" for the National Health Service.

- **NOVARTIS/SANDOZ** recalled 24 lots of methotrexate because of glass particulates that were found in 50 mg/2 mL and 250 mg/10 mL vials.

- **Pulmonary vein isolation –** The U.K.'s NICE plans to review the use of endoscopic laser balloon pulmonary vein isolation procedures in preventing atrial fibrillation.

- **SANOFI-AVENTIS** is acquiring **BMP Sunstone**, a large Chinese consumer healthcare company which sells children's cold medicines, vitamins, supplements, etc.

- **SUNOVION PHARMACEUTICALS' Latuda (lurasidone)**, another atypical schizophrenia drug, was approved by the FDA.

- **Tamoxifen –** A survey of British oncologists and surgeons published in the ***Journal of Clinical Oncology*** found that many of these doctors are not yet convinced of the importance of doing genetic testing to identify patients with the CYP2D6 genotype before prescribing tamoxifen to prevent breast cancer recurrence. However, doctors do agree that women taking tamoxifen should avoid concomitant medications that are CYP2D6 inhibitors.

- **THERMO FISHER SCIENTIFIC's Spectra MRSA test –** The company was given clearance by the FDA to market the test (which yields results within one day) for use in testing blood samples. Previously, the test was approved for use with nasal samples.

- **VIROPHARMA's Cinryze (complement C1 esterase inhibitor) –** The FDA rejected expanded manufacturing, asking for more information before approving the scale-up for this infusion therapy for hereditary angioedema. The company had hoped to begin increased production of this FDA-approved orphan drug in 1Q11.

NEWS IN BRIEF

Alzheimer's disease (AD) – possible new target

Striatal-enriched tyrosine phosphatase (STEP) appears to be a promising target for AD drug therapy. In a study published in ***PNAS***, deletion of this gene restored cognition and repaired synapses in AD transgenic mice – without reducing amyloid-β or tau pathology.

STEP is a brain-specific tyrosine phosphatase. Timing of therapy may be a hurdle, however, because STEP-targeted therapy may protect loss of neurodegeneration but not restore

lost cognition. So, it is unclear how helpful it will be in advanced AD.

There also are unpublished data showing that STEP therapy might have a role in other disorders. For instance, STEP is elevated in Fragile X syndrome and schizophrenia, and reducing STEP alleviated symptoms in a Fragile X mouse model.

AMAG PHARMACEUTICALS – problems mounting

AMAG received a warning letter from the FDA for reportedly promoting unapproved uses – and omitting risks – on its website for Feraheme (ferumoxytol), an injectable anemia drug, and GastroMark, an MRI contrast agent. AMAG has removed the offending web pages. The company is laying off 24% of its workforce to cut costs. And the company is in discussions with the FDA over hypersensitivity and anaphylaxis reactions with Feraheme, which could lead to a boxed warning (black box).

AMPHASTAR PHARMACEUTICALS – fighting the FDA

Amphastar, which is trying to develop a generic Sanofi-Aventis's Lovenox (enoxaparin), sued the FDA, challenging the FDA's authority to quarantine two shipments of Chinese-manufactured heparin last summer. Amphastar claims the heparin was being transferred between subsidiaries of the same company and was intended for research, not for treating humans, so the FDA did not have the right to stop the shipments. *Does anyone ever really win fighting the FDA?*

ARENA PHARMACEUTICALS' Lorqess (lorcaserin) – rejected by FDA

The FDA rejected this diet drug, saying safety concerns outweighed the drug's "marginal" effectiveness (~3% weight loss). The biggest issue was tumorgenicity in rats. The FDA said additional safety studies may be needed, but at the FDA advisory committee meeting on the drug, an FDA toxicologist suggested that even a two-year animal study in another species would not be sufficient. Arena plans to meet with the FDA to see if there is a way forward, but that looks murky.

AVANIR PHARMACEUTICALS' Nuedexta (quinidine + dextromethorphan) – finally gets FDA approval

Nuedexta was approved by the FDA to treat pseudobulbar affect (uncontrolled laughing and crying) in patients with neurological disorders. The expectation is that it will be particularly useful in multiple sclerosis and amyotrophic lateral sclerosis (ALS). In 2006, the FDA rejected Nuedexta (formerly known as AVP-923 and Zenvia) because of concerns about QT prolongation, but the company reformulated it with a lower dose of quinidine and resubmitted it.

B. BRAUN MEDICAL – a new heparin recall, same contaminant

Braun recalled seven lots of heparin because of possible contamination with oversulfated chondroitin sulfate, the contaminant that caused a heparin recall (and several deaths) in 2008. Scientific Protein Laboratories, which was involved in the previous contamination crisis, reportedly also was involved in the manufacture of Braun's heparin.

EXACT SCIENCES – developing test to predict CRC

A 1,100-patient validation study presented at the American Association for Cancer Research conference on Colorectal Cancer (CRC) found this investigational, non-invasive, DNA methylation stool test detected 64% of CRC pre-cancers (>1 cm) and 85% of cancers (87% of State I-III and 69% of Stage IV). Positive test results would be followed up with a colonoscopy. The test, which is not yet approved by the FDA, is conducted using a stool sample and works by detecting tumor-specific DNA alterations in cells that are shed into the stool from pre-cancerous or cancerous lesions.

Fibrates – not first-line therapy in Europe

The EMA's Committee for Medicinal Products for Human Use said fibrates have a role in treating high cholesterol, but they shouldn't be the first-line therapy. Rather, they should be reserved for patients who have severely high triglycerides or are intolerant to statins. However, the committee concluded that the benefits of fibrates outweigh the risks – at least for the time being. The committee's recommendations still need to be formally adopted by the EMA to go into effect.

Gene patents – government now says they are not patentable

The Department of Justice deciding now that human and other genes should ***not*** be able to be patented. The new position came in a friend-of-the-court brief in a case challenging patents by Myriad Genetics and the University of Utah Research Foundation on the BRCA1 and BRCA2 genes used to determine a woman's risk of breast and ovarian cancer.

The new government position is contrary to the U.S. Patent and Trademark Office position, so it is not clear whether gene

patents will continue to be issued, at least in the near term. The government said that isolating a gene – without further altering or manipulating it – does not change its nature, so it is not patentable, comparing an isolated gene to cotton fibers separated from cotton seeds or coal extracted from the earth. However, the Justice Department lawyers suggested that if genes are manipulated, as with genetically modified crops or gene therapies, they could still be patented.

Infectious Disease Society of America (IDSA)

- **OPTIMER PHARMACEUTICALS' fidaxomicin – may reduce relapses in *C. difficile* diarrhea.** A pooled analysis of 1,164 patients from two studies was presented at IDSA, and it showed this macrocyclic antibiotic (at a dose of 200 mg BID) had the same cure rate as standard therapy with vancomycin 125 mg QID (88% vs. 86%) and a similar adverse event profile but a significantly lower relapse rate – 13% vs. 24% at 40 days post-treatment.
- **PFIZER's Zithromax (azithromycin) – beats Cipro in cholera.** A single dose of azithromycin outperformed six doses of Bayer's Cipro (ciprofloxacin) for the treatment of cholera in a randomized double-blind trial.
- **PFIZER's Zyvox (linezolid) – beats vancomycin in MRSA.** A randomized, double-blind, 1,200-patient, Phase IV trial found that IV Zyvox was more effective in treating hospital-acquired pneumonia due to methicillin-resistant MRSA – 57.6% vs. 46.6% cure rate. However, mortality was comparable.
- **Tenofovir gel – protects women from AIDS virus.** According to the researchers, the FDA has given this gel fast-track status and will only require a "limited amount" of new information about safety and efficacy before it can be submitted for approval. Gilead licensed tenofovir for use in the gel to CONRAD, a division of the Eastern Virginia Medical School, which has partnered with the Centre for the AIDS Programme of Research in South Africa (CAPRISA) and the U.S.-based Family Health International.

Interventional cardiology – impediments to radial access

A ***CRTonline.org*** poll of interventional cardiologists, found that increased use of radial access for stenting depends on:

- 35% improved diagnostic and guiding catheters.
- 45% more training.
- 20% more data on the superiority to the femoral approach.

INTUITIVE SURGICAL's da Vinci robot – useful for myomectomy

Removing myomas laparoscopically using the da Vinci robot may have some advantages over conventional laparoscopy or open removal, according to a retrospective study reported at the American Society for Reproductive Medicine. Researchers analyzed data from 575 myomectomies performed by two surgeons at the Cleveland Clinic from 1995 to 2009, including two years of data on the robotic approach: 68% were open procedures, 16% were laparoscopic, and 16% were robot-assisted. (*See chart below*)

LILLY and MERCK KgaA's Erbitux (cetuximab) – maybe KRAS isn't definitive in CRC after all

Erbitux helped a group of colorectal cancer (CRC) patients thought to be immune to the treatment because of their KRAS status. The retrospective study of 579 CRC patients treated with Erbitux, published in the ***Journal of the American Medical Association***, contradicts earlier assumptions about the way Erbitux works in KRAS mutant patients. In this study, KRAS mutant CRC patients had longer survival with Erbitux + chemotherapy than wild-type KRAS patients. The Belgian researchers concluded that KRAS mutation alone "may not be a black-and-white test for whether patients will be helped by Erbitux."

da Vinci Robot in Myomectomy

Measurement	da Vinci	Laparoscopy	Open procedure
Greater number, diameter, and weight of myomas removed	p<0.05	---	p<0.05
More broad ligament and submucous myomas removed	p<0.05	---	---
More intramural myomas removed	p<0.05	---	p<0.05
Less blood loss	p<0.001	p<0.001	---
Transfusions required	2.2%	0	6.4%
Longer surgical time	p<0.001	p<0.001	---
Hospital stay	1 day p<0.001	1 day p<0.001	3 days
Postoperative complications	---	1 bowel injury that required conversion to laparotomy; 1 postop pyrexia	1 wound separation

NOVO NORDISK's degludec and degludecPlus – comparable efficacy, less hypoglycemia

The company released data from a 26-week Phase IIIa study in Type 2 diabetics in which this ultra long-acting insulin met its primary endpoint, showing non-inferiority to Sanofi-Aventis's Lantus (insulin glargine) in lowering HbA_{1c} similarly (~7.2% with both) but with less hypoglycemia.

The company also reported the results of a Phase IIIa study with degludecPlus, a three-times-a-week version of degludec in patients with "late-stage" Type 2 diabetes. In that study, degludecPlus also showed non-inferiority on efficacy to NovoMix 30 BID, when both were added to standard oral anti-diabetic drugs (7.1% drop in HbA_{1c} in both groups). DegludecPlus patients also had a lower average total daily insulin dose.

NOVO NORDISK's Victoza (liraglutide) – obesity program resumed, data positive

The company resumed studying Victoza as an obesity drug this past summer, and the first Phase III data – from the 422-patient SCALE trial – was released, showing that patients who had already lost 5% of their body weight on a low-calorie diet during the 4- to 12-week run-in period went on to lose an additional 6 kg (13 pounds) with 3.0 mg Victoza vs. placebo at 56 weeks. Adverse events (mostly GI) were the same as seen in diabetics.

PFIZER's crizotinib (PF-02341066) – positive data continue to build

Part 2 expansion data from an open-label, multicenter Phase 1 trial (A8081001) were published in the ***New England Journal of Medicine***, and the data showed that 57% of ALK-positive patients with non-small cell lung cancer (NSCLC) had either a complete (one patient) or partial (46 patients) response to treatment with 250 mg BID crizotinib. The most common adverse events were nausea, diarrhea, vomiting, and mild visual disturbances. Grade 3 liver enzyme elevations occurred in four patients. One patient experienced a Grade 4 ALT elevation, and one patient discontinued treatment due to Grade 3 ALT increases.

About 3%-5% of NSCLC tumors are ALK-positive. The Part 1 data from this study were presented in June 2010 at the American Society of Clinical Oncology (ASCO) meeting, and additional results were reported at ESMO (European Society for Medical Oncology). An open-label Phase III trial (PROFILE-1007 or A8081007) vs. standard chemotherapy is ongoing.

Pfizer plans to submit crizotinib to the FDA in 1H11 ***along with*** a gene diagnostic test being developed by Abbott to identify the patients most likely to benefit from the drug.

Prostate drugs – safety and efficacy review

The FDA's Oncologic Drugs Advisory Committee (ODAC) will meet on December 1, 2010, to consider an expanded label for GlaxoSmithKline's Avodart (dutasteride), and the panel also will discuss the efficacy and safety of both Avodart and Merck's Proscar (finasteride), given the findings in the PCPT trial: a statistically significant reduction in the 7-year prevalence of prostate cancer with Proscar but more aggressive cancers in the Proscar arm than with placebo.

VIVUS's Qnexa (phentermine + topiramate) – rejected by FDA

The FDA rejected this diet drug, issuing a complete response letter that cited problems with heart rate and pregnancy risks (birth defect concerns). The FDA decision was not unexpected since the FDA's advisory committee voted 10-6 against approval. *Remember: women who lose weight tend to be more fertile.*

However, a company official at a Qnexa poster at the American Association for the Study of Liver Diseases (AASLD) put a positive spin on the FDA letter, saying, "At least we have a clear path forward." What does that mean? Perhaps some wishful thinking. She said the FDA wants to see the SEQUEL trial data, which is completed, as well as "a review of all available data on heart rate and teratogenicity. The Agency wants an evidence-based review of the relationship between heart rate change and cardiovascular outcomes – for labeling and REMS (Risk Evaluation and Management Strategy) information…We already committed to a pregnancy registry."

REGULATORY NEWS

New FDA drug guidance

The FDA is preparing to collect comments on a draft guidance that could change how drug reviews are handled. In an effort to create a more consistent review process, the FDA plans to provide guidance on tools and tests used to give an early indication of a drug's effect on patients instead of evaluating the new tools on a case-by-case basis as it is now doing. The FDA also is encouraging pharmas to form collaborative groups to work together to develop tools, noting that projects coordinated through a consortia can "make the process easier on developers and on [the FDA]."

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
	November 2010	
November 2-3	Draft of regulations for **generic biologics**	FDA public hearing
November 4-5	Public workshop on **orphan drugs**	FDA public workshop in Lansdowne VA
November 16	**GSK/Human Genome Sciences' Benlysta** (belimumab) for lupus	FDA's Arthritis Advisory Committee
November 18	**Amgen's denosumab** for cancer patients	PDUFA date
November 18	**Mela Sciences' MelaFind** for melanoma detection	FDA's General and Plastic Surgery Devices Advisory Committee
November 30	**GlaxoSmithKline/Valeant's ezogabine** for epilepsy	PDUFA date
	December 2010	
December 1	**GlaxoSmithKline's Avodart** (dutasteride) and **Merck's Proscar** (finasteride) for prostate cancer	FDA's Oncologic Drugs Advisory Committee (ODAC)
December 2	**Bristol-Myers Squibb's Yervoy (ipilimumab)** for advanced melanoma; and **iPR Pharmaceuticals/AstraZeneca's Zictifa** (vandetanib) for unresectable, locally-advanced or metastatic medullary thyroid cancer	FDA's Oncologic Drugs Advisory Committee (ODAC)
December 2	**Oceana Therapeutics' Solesta** (dextranomer in gel of stabilized non-animal hyaluronate) for fecal incontinence	FDA's Gastroenterology and Urology Devices Advisory Committee
December 3	**Allergan's Lap-Band**, expanded indication	FDA's Gastroenterology and Urology Devices Advisory Committee
December 7	**Orexigen Therapeutics' Contrave** (naltrexone + bupropion), a diet drug	FDA's Endocrinologic and Metabolic Drugs Advisory Committee
December 9	**GSK/Human Genome Sciences' Benlysta** (belimumab) for lupus	PDUFA date
December 16	**AstraZeneca's Brilinta** (ticagrelor), an anticoagulant	PDUFA date
December 25	**Bristol-Myers Squibb's ipilimumab** for advanced melanoma	PDUFA date
	January 2011	
January 7, 2011	**Endo Pharmaceuticals' tamper-resistant Opana ER** (oxymorphone), a painkiller	PDUFA date
January 31, 2011	**Orexigen Therapeutics' Contrave** (naltrexone + bupropion), a diet drug	PDUFA date
	Other future meetings	
March 7, 2011	**Salix Pharmaceuticals' Xifaxan** (rifaximin) for non-constipation IBS	PDUFA date
Date TBA, 2011	Review of **accelerated drug approval process**	FDA's Oncologic Drugs Advisory Committee (ODAC)
Summer 2011	Report on **FDA 510(k) reform**	Institute of Medicine