TRENDS-in-MEDICINE

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Quick Takes

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

Trends-in-Medicine
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SHORT TAKES

- **ABBOTT LABORATORIES** is moving production of two anti-inflammatory drugs from Greece to Serbia. An Abbott subsidiary signed a manufacturing agreement with Serbian state-run drugmaker **Galenika**, which has completed construction on a state-of-the-art manufacturing facility.

- **ARENA PHARMACEUTICALS/EISAI's Lorqess (lorcaserin) –** After meeting with the FDA, the companies said they plan to resubmit this diet drug by the end of 2011 following additional testing, presumably animal testing. The FDA rejected Lorqess in October 2010, citing questions about cardiac safety and animal carcinogenicity. The valvulopathy seen in a diabetic study still casts a shadow over the regulatory outlook.

- **ASTRAZENECA/MEDIMMUNE's motavizumab –** The company has pulled the plug on development of motavizumab in respiratory syncytial virus (RSV) but will continue investigating it in other diseases. In August 2010, the FDA issued a second complete response letter, saying it wanted another RSV study showing a satisfactory risk:benefit profile before approving it.

- **BIOGEN IDEC** acquired a **Neurimmune** subsidiary that gives Biogen the worldwide rights to three preclinical immunotherapy programs with central nervous system (CNS) targets – alpha-synuclein, tau, and TDP-43 – thought to be important in neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, and amyotrophic lateral sclerosis (ALS). Biogen will be responsible for testing the drugs and handling sales if and when they are approved.

- **BIOGEN IDEC/ELAN's Tysabri (natalizumab) –** The companies are asking the FDA and the European Medicines Agency (EMA) to revise the label for this multiple sclerosis therapy to cite anti-JC virus antibody positivity as a potential risk factor for progressive multifocal leukoencephalopathy (PML). *Remember, the FDA has had a safety review of Tysabri underway for several months.*

- **CHELSEA THERAPEUTICS' Northera (droxidopa) –** The company plans to file Northera, a synthetic catecholamine that is directly converted to norepinephrine (NE) via decarboxylation, for symptomatic neurogenic orthostatic hypotension in 2Q11 based on two Phase III trials (Studies 301 and 302). Chelsea said the FDA is ***not*** requiring Study 306, another pivotal study, for approval.

- **FRESENIUS KABI's red blood cell exchange sets –** The FDA issued a Class I recall on these devices which are used on AS104 blood cell separation devices for apheresis because they were found to remove greater amounts of red blood cells than intended, resulting in hemodilution. The recall follows a Field Safety Corrective Action letter that

the company issued on October 18, 2010. Customers are instructed to discontinue distributing, using, and dispensing the products and return them to the company.

- **GILEAD SCIENCES** is getting its first monoclonal antibody with the purchase of **Arresto Biosciences.** Arresto's lead product, AB-0024, is an antibody for cancer and idiopathic pulmonary fibrosis (IPF).

- **HELM AG** bought an interest in **Amarin Technologies**, which has transdermal delivery system technology. The two companies have been cooperating on the development of a pain release patch.

- **IMPAX PHARMACEUTICALS' IPX-066 (extended release carbidopa/levodopa) – GlaxoSmithKline (GSK)** signed a deal to co-develop this late-stage Parkinson's disease compound outside the U.S. Impax will complete the current Phase III program, with results expected in 2011. In the U.S. Impax expects to file a New Drug Application (NDA) in late 2011 and will be responsible for commercialization. In other regions, excluding Taiwan, GSK will be responsible for further development, registration, and commercialization.

- **INTERMUNE's Esbriet (pirfenidone)** gained approval support from the European Committee for Medicinal Products for Human Use for the treatment of idiopathic pulmonary fibrosis (IPF), though the FDA rejected it earlier this year.

- **JOHNSON & JOHNSON/CENTOCOR/JANSSEN's abiraterone acetate** was submitted to the FDA for approval to be administered with prednisone for the treatment of advanced metastatic prostate cancer in patients who had prior taxane-based chemotherapy. The PDUFA date is October 20, 2011. Abiraterone was also submitted to the EMA.

- **MEDTRONIC's Arctic Front** received FDA approval for atrial fibrillation cryoablation.

- **MERCK's Gardasil (HPV vaccine)** was approved by the FDA for the prevention of anal cancer and associated precancerous lesions due to human papillomavirus (HPV) types 6, 11, 16, and 18 in people ages 9-26. The vaccine already is approved to prevent cervical, vulvar, and vaginal cancer in females and genital warts in both males and females.

- **MESA LABORATORIES**, which makes instruments and disposable products for healthcare and industrial applications, acquired the biological indicators business of **Apex Laboratories**. Biological indicators are used to ensure that conditions in enclosures are appropriate to achieve a proper level of decontamination.

- **ONCOLYS BIOPHARMA's festinavir – Bristol-Myers Squibb** is buying exclusive worldwide rights to develop, make, and sell this next-generation nucleoside reverse transcriptase inhibitor for HIV. The companies said early studies indicated festinavir may be safer than previous-generation HIV drugs.

- **PFIZER's Lipitor (atorvastatin) –** Pfizer announced another Lipitor recall, this time ~19,000 bottles, again due to a "musty odor." The company said the odor is consistent with the presence of tribromoanisole (TBA), a chemical linked to a wood preservative used in shipping pallets.

- **ROYAL DSM NV**, a Dutch chemicals company with a large nutritional supplement business, plans to buy **Martek Biosciences** to boost its presence in the U.S. and improve its infant formula products. Martek's key product is DHA, an omega-3 fatty acid added to infant formula.

- **VIVUS's Qnexa (phentermine + topiramate) –** Despite the FDA rejection, Vivus submitted Qnexa to European regulators.

NEWS IN BRIEF

ABBOTT

- **Certriad (TriLipix + Crestor) – development discontinued.** Abbott and **AstraZeneca** terminated this cholesterol-lowering combination drug. The results of the ACCORD trial in March 2010 showed that adding a fibrate (e.g., TriLipix) to a statin (e.g., Crestor) did not reduce cardiovascular events, and shortly after that the FDA issued a complete response letter for Certriad.

- **Glucose test strips – recalled.** Strips produced between January and May 2010 are being recalled because the FDA says they may give falsely low blood glucose results, leading patients to try to raise their blood glucose unnecessarily or to fail to treat elevated blood glucose because of a false, low reading. The problem is the test strips' inability to absorb enough blood for monitoring, especially if the strips were exposed to warm weather or prolonged storage. The company's blood glucose monitoring systems are not affected by the recall.

ALIMERA SCIENCES' Iluvien (fluoroquinolone insert) – rejected by FDA

The FDA issued a complete response letter for this back-of-the-eye implant for diabetic macular edema, citing several safety and efficacy issues. The FDA said it wanted:

- 36-month data, including new exploratory analyses. The company submitted 24-month data from the FAME study

(which was made up of two Phase III trials), but it has been following those patients longer, so that data will be available. The company said no new clinical studies were requested.

- Additional manufacturing, packaging, and sterilization information.
- Resolution of deficiencies its inspectors found in current good manufacturing practices (cGMP) at two of Alimera's third-party manufacturers.

Atrial fibrillation (AFib) – new guidelines issued

New guidelines for AFib were created by the American College of Cardiology (ACC), American Heart Association (AHA), and the Heart Rhythm Society and published in ***Circulation*** and in the ***HeartRhythm*** journal. Among the key features of the guidelines were:

- **Rate.** Strictly controlling heart rate (<80 bpm at rest) provides no advantage over more lenient heart rate control (<110 bpm at rest) in patients with persistent AFib and stable ventricular functioning.
- **Plavix (Sanofi-Aventis, clopidogrel).** This "might be considered" in patients who are poor candidates for warfarin.
- **Multaq (Sanofi-Aventis, dronedarone).** This "could reduce hospitalizations for cardiovascular events" but should not be given to patients with NYHA Class IV heart failure or patients with an episode of decompensated heart failure in the past four weeks.
- **Catheter ablation.** The recommendations support a role for this treatment in selected patients at experienced centers (where >50 cases are performed annually).

CYCLACEL PHARMACEUTICALS' seliciclib – mixed results in Phase IIb trial

Top-line results from the randomized, double-blind, placebo-controlled, 53-patient, Phase IIb APPRAISE trial at 21 U.S. sites found this oral therapy missed the primary endpoint, which was progression-free survival (PFS), but showed a survival benefit vs. placebo in third-line (or later) therapy for NSCLC. PFS was 48 days with seliciclib vs. 53 days with placebo. However, median overall survival favored seliciclib (388 days vs. 218 days). The company said it plans to collect and analyze available biopsy samples from the trial to determine whether there is a biological basis for the difference between PFS and overall survival.

Enrollment in this trial was stopped early because the independent data review committee concluded that PFS efficacy was futile. Since there was no safety concern noted, the patients in the study were allowed to continue. Thus, the company would need to do another trial, probably with overall survival as the primary endpoint, for FDA approval.

Fingerprints – will they be needed for prescription drugs?

An ordinance has been proposed in Peoria, Arizona, that would require patients – or anyone picking up a prescription for a family member or friend – to be fingerprinted at a pharmacy when picking up a prescription for commonly abused drugs, such as Purdue's OxyContin. Peoria City Attorney Stephen Kemp plans to present details of the proposal to the Arizona State Board of Pharmacy in January 2011.

Growth hormone – now a U.S. safety review

As ***Quick Takes*** speculated in the December 12, 2010, issue, the FDA decided to follow the lead of the EMA and initiate its own safety review. A French study (SAGhE) found that people with idiopathic growth hormone deficiency and idiopathic or gestational short stature who were treated with recombinant human growth hormone during childhood were at a small, increased, long-term risk of death compared to the general French population, especially at higher-than-recommended doses. In the U.S. somatropin products include: Lilly's Humatrope, Merck KGaA's Saizen and Serostim, Novartis/Sandoz's Omnitrope, Novo Nordisk's Norditropin, Roche's Nutropin, and Teva's Tev-Tropin.

IMCLONE/MERCK KGAA's Erbitux (cetuximab) – rash is predictive of response in NSCLC

In a study published in ***Lancet Oncology***, German researchers found that non-small cell lung cancer (NSCLC) patients who develop an acneiform rash when taking the first cycle of Erbitux are the patients most likely to respond to the drug. Survival was almost twice as long for patients with first-cycle rash vs. patients with no rash (15 months vs. 8.8 months). The rash also predicted improved PFS (5.4 months vs. 4.3 months) and a higher response rate (44.8% vs. 32%).

INCYTE's INCB-018424 – positive Phase III results in myelofibrosis

The company released top-line data from a 24-week, 309-patient Phase III trial in myelofibrosis, and this JAK inhibitor shrank spleen size by ≥35% in 42% of patients while only 1%

of placebo patients achieved that goal. The main side effects were anemia and thrombocytopenia. The results of a second Phase III trial being run by partner Novartis are expected in early 2011.

Percutaneous coronary interventions (PCIs) – counting method changed

The America Heart Association has adopted a new method of counting angioplasties and PCIs that avoids duplication. Now, if a single procedure includes both balloon angioplasty and a stent (which occurs in ~90% of procedures), it will only be counted as one procedure.

The AHA's statistics are widely cited, so the change in counting method is important. For example, 1.3 million PCIs were reported for 2006, but with the new method only ~600,000 will be listed for 2007. This will correlate more closely with the way the Agency for Healthcare Research and Quality (AHRQ) counts PCIs; it said 688,000 PCIs were performed in 2007.

REGENERON PHARMACEUTICALS/BAYER's VEGF Trap-Eye – positive Phase III results in macular edema

The companies said the drug met the primary endpoint in a 114-patient Phase III trial in patients with macular edema because of central retinal vein occlusion, with 56.1% of patients who got monthly intravitreal Trap-Eye injections gaining ≥15 letters in vision vs. 12.3% of placebo patients. The companies plan to submit Trap-Eye to both the FDA and EMA for treatment of wet age-related macular degeneration (AMD) in 1H11.

ROCHE/GENENTECH's Lucentis (ranibizumab) – doctors warned to be careful with usage rebates

While Lucentis is approved to treat wet AMD, many ophthalmologists use another Roche/Genentech drug off-label instead, Avastin (bevacizumab), in the belief that it works as well at a small fraction of the cost. The National Eye Institute is running a trial comparing the two drugs.

Genentech currently offers a rebate program for the top prescribers of Lucentis, and the American Academy of Ophthalmology (AAO) is concerned that these "substantial incentives" may influence decision making "by introducing a potential source of bias in the selection of drugs for AMD." Thus, the AAO, with support of the American Society of Retina Specialists, the Retina Society, and the Macula Society, is preparing an educational article for its monthly magazine, ***EyeNet***, that will discuss the ethical ramifications of this and similar rebate programs having the potential to influence clinical care and decision making. The piece also will be posted on the Academy's website.

The educational article will cite the Academy's existing ethics and disclosure advice, reminding ophthalmologists that their clinical judgment and practice must not be affected by economic interests, that conflicts must be disclosed, and that sanctions can be imposed for violations of these rules.

The AAO noted that while volume-based rebate programs or volume-based price discounting arrangements are common – and often legal – they become a concern if and when they have the potential to directly impact a physician's decision making and "are problematic for physicians from an ethical (and sometimes legal) perspective."

SANOFI-AVENTIS

- **Buying technology from Ascendis Pharma** for extended-release drug delivery for use with diabetes medicines (i.e., insulin).
- **Genetic testing questions resurface for Plavix (clopidogrel)** – A German study published in ***Nature Medicine*** found that the paraoxonase-1 (PON1) enzyme (particularly PON1 QQ192) is critical for the activation of Plavix, raising questions – again – about whether patients should have genetic testing before taking Plavix long term, as the FDA has recommended but not required. The researchers found that 75% of the variability in Plavix response could be attributed to PON1 status.

REGULATORY NEWS

Biomarker devices – FDA and DARPA workshop planned

The FDA and the Defense Advanced Research Projects Agency (DARPA) will cosponsor a public workshop on February 9, 2011, on expanding *in vivo* biomarker detection devices. The workshop will focus on current state-of-the-art and innovative research opportunities with *in vivo* analytical devices capable of measuring biomarkers that characterize normal biological processes, pathologic processes, and pharmacologic responses. In particular, the workshop will discuss the technical challenges for developing implanted or continuously applied devices that measure/monitor clinically relevant molecular biomarkers (small molecules, proteins, peptides, and nucleic acids) to alert the user of the need for clinical attention and/or to inform the clinician with regard to appropriate action.

FDA 510(k) reform – impact study being launched

Researchers from Northwestern University and Stanford University are conducting a comprehensive study to get input about problems facing both the FDA and the medical device industry as the 510(k) process is reformed. The ~90-question electronic survey, funded by the non-profit Institute for Health Technology Studies (InHealth), will collect information, data, and "constructive" input from people who have been actively involved in the design and development of regulated medical products: entrepreneurs, academic physician-inventors, and federal regulators.

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest
(items in RED are new since last week)

Date	Topic	Committee/Event
	December 2010	
December 29	**Mannkind's Afresa** (inhaled insulin)	PDUFA date
	January 2011	
January 7	**Endo Pharmaceuticals' Opana TRF** (oxymorphone ER) for pain	PDUFA date
January 7	**AstraZeneca's vandetanib** for thyroid cancer	PDUFA date
January 12	**Alnara Pharmaceuticals' Solpura** (liprotamase capsules) for exocrine pancreatic insufficiency due to cystic fibrosis, chronic pancreatitis, pancreatectomy, etc.	FDA's Gastrointestinal Drugs Advisory Committee
January 19	**Erythropoiesis stimulating agents (ESAs)** for anemia in adults with CKD	CMS Medicare Evidence Development & Coverage Advisory Committee (MEDCAC)
January 20	**Avid Radiopharmaceuticals' florbetapir F-18 injection** for β-amyloid measurement in Alzheimer's disease	FDA's Peripheral and Central Nervous System Drugs Advisory Committee
January 21	**Bayer's gadobutrol injection**, an MRI contrast agent for brain and CNS imaging	FDA's Peripheral and Central Nervous System Drugs Advisory Committee
January 27-28	Discussion of **possible reclassification of electroconvulsive therapy devices**	FDA's Neurological Devices Advisory Committee
January 31	**Orexigen Therapeutics' Contrave** (naltrexone + bupropion), a diet drug	PDUFA date
	Other future 2011 meetings	
February 9	**Bristol-Myers Squibb's Yervoy** (ipilimumab) for the treatment of advanced melanoma in patients who have received prior therapy	FDA's Oncologic Drugs Advisory Committee (ODAC)
February 9	Public workshop on expanding ***in vivo* biomarker detection devices**, focusing on research opportunities and technical challenges	FDA and the Defense Advanced Research Projects Agency (DARPA)
March 5 (approx.)	**Merck KGaA's cladribine** for multiple sclerosis	PDUFA date
March 7	**Salix Pharmaceuticals' Xifaxan** (rifaximin) for non-constipation IBS	PDUFA date
March 10	**Human Genome Sciences/GSK's Benlysta** (belimumab) for lupus	PDUFA date
March 26	**Bristol-Myers Squibb's Yervoy** (ipilimumab) for advanced melanoma	PDUFA date
April 10	Open forum to discuss statistical issues related to **drug and biologics development and review**	Joint FDA and Drug Information Agency Forum
Summer	Report on **FDA 510(k) reform**	Institute of Medicine
October 20	**Johnson & Johnson's abiraterone** for metastatic prostate cancer	PDUFA date
Date TBA	Review of **accelerated drug approval process**	FDA's Oncologic Drugs Advisory Committee (ODAC)