TRENDS-in-MEDICINE

January 16, 2011

by Lynne Peterson

Quick Takes

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

SHORT TAKES

- **ABBOTT's briakinumab (ABT-874)** – The company withdrew both the U.S. and European applications for this IL-12/23 inhibitor for psoriasis. Based on regulatory feedback, Abbott is evaluating whether additional data analysis or even more studies will be needed due to a cardiovascular risk signal seen in the Phase III studies. In addition, development in Crohn's disease, which was in Phase II, has been terminated.

- **BIOCON's IN-105** missed the primary endpoint, failing to lower HbA_{1c} by ≥0.7% vs. placebo. The company speculated that this may be due to placebo patients modifying their behavior during the study. *Secondary efficacy and safety targets were met, so perhaps the company won't give up on IN-105.*

- **BIOCRYST PHARMACEUTICALS' peramivir** – The company petitioned the Department of Health and Human Services (HHS) to extend a Phase III trial of this intravenous flu drug beyond the end of the year. BioCryst also asked for additional funding to increase the study's sample size and clinical sites. In addition, BioCryst wants to revise the study's primary efficacy endpoint so it can compare patients treated with peramivir to patients who have not been treated with a neuraminidase inhibitor.

- **BIOGEN IDEC's fampridine** – Biogen has the OUS rights to this therapy to improve walking in multiple sclerosis (MS) patients, but getting OUS regulatory approval hasn't been easy. Canadian regulators (Health Canada) issued a letter of deficiency for this recently, and the European Medicines Agency (EMA) previously questioned the company's application. In the U.S., Acorda Therapeutics has FDA approval for fampridine (Ampyra).

- **C.R. BARD/DAVOL's XenMatrix**, a surgical graft used in abdominal wall and hernia repair, was voluntarily withdrawn from the market after the product failed to meet the FDA's standards for endotoxin concentrations.

- **CORCEPT THERAPEUTICS' Corlux (mifepristone)** – The company previously said this treatment for Cushing's syndrome met the primary endpoint (improving glucose tolerance and blood pressure) in a Phase III trial. Now, the company says the drug also met secondary endpoints, including changes in diabetes and hypertension medications, insulin sensitivity, and weight. Corcept plans to submit Corlux, which already has orphan drug status, to the FDA in 1Q11.

- **DENDREON's Provenge (sipuleucel-T)** – The company plans to submit this prostate cancer immunotherapy to European regulators late this year or in early 2012. The company expects to have a contract manufacturer to produce Provenge until it establishes a plant in central Germany.

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- **DISCOVERY LABS' Surfaxin (lucinactant)** – The FDA asked the company for more information to finalize the design of a quality control and stability test for this drug to treat respiratory problems in infants. Surfaxin was initially denied in 2009 over questions about procedures for testing shelf-life viability. The FDA now wants Discovery Labs to increase the sample size and test additional batches of Surfaxin. The company plans to respond to the FDA by 3Q11.

- **ENDO PHARMACEUTICALS' Opana TRF (oxymorphone ER)** – The FDA rejected this tamper-resistant formulation of Opana, an opioid painkiller. The company said the FDA is not requesting any additional trials. The FDA concern apparently is related to the crush-resistance. Endo expects to re-file by mid-2011.

- **EPIZYME** signed a drug development deal with **GlaxoSmithKline**, focusing on cancer therapies and other diseases. The companies have formed a strategic alliance to develop epigenetic therapeutics.

- **EXELIXIS's XL-184**, a treatment for a rare thyroid cancer, was granted orphan drug status by the FDA. The company expects to submit it to the FDA in 2H11.

- **GILEAD SCIENCES' elvitegravir** – The company, at the recommendation of the FDA, is doubling the length of the pivotal Phase III trial for this HIV antiviral, but Gilead said this will not affect trials of the 4-drug cocktail (elvitegravir, cobicistat, Truvada) it has in development.

- **HOLOGIC**, which makes mammography systems and other diagnostic equipment, bought **Interlace Medical**, which makes the MyoSure hysteroscopic tissue removal system for removing fibroids and polyps.

- **HUMAN GENOME SCIENCES** is looking for partnerships and acquisitions in cancer and autoimmune disorders.

- **IDEX** is acquiring **Microfluidics International**, which makes equipment that laboratories and commercial companies use to make materials for the drug and chemical markets.

- **LILLY and BOEHRINGER INGELHEIM** are collaborating on diabetes drugs, including two oral agents – Boehringer's linagliptin and BI-10773 – as well as Lilly's basal insulin analogs LY-2605541 and LY-2963016.

- **PFIZER and SUTRO BIOPHARMA** will collaborate on the research and development of biotechnology drugs. Sutro gives Pfizer access to peptides that have been difficult to produce using conventional technology.

- **PFIZER's crizotinib (PF-02341066)** – Pfizer has initiated a rolling submission to the FDA on this therapy for ALK-positive non-small cell lung cancer (NSCLC) and expects to complete the submission, which has fast track status, in 1H11.

- **QIAGEN** is acquiring a stake in **Alacris Theranostics**, which is developing individualized cancer treatment strategies based on a patient's genomic profile, using a proprietary modeling system, ModCell, developed by researchers at the Max Planck Institute for Molecular Genetics and at Harvard Medical School. The deal gives Qiagen an exclusive option to access all biomarkers emerging from this discovery program.

- **RITE-DENT MANUFACTURING** – The FDA seized all the dental devices of this Florida manufacturer, saying the company had failed to resolve continuing and significant manufacturing violations.

- **ROXANE LABORATORIES' morphine sulfate 100 mg/5 mL** – The company and the FDA notified healthcare professionals of serious adverse events and deaths resulting from accidental overdoses of this high-potency oral opioid solution. The problem generally has been that solutions ordered in milligrams (mg) were mistakenly interchanged for milliliters (mL). New product labeling and packaging have been approved that should reduce the risk of these medication errors.

- **SAVIENT PHARMACEUTICALS' Krystexxa (pegloticase)** – The company said two contract manufacturing firms making this gout medicine – Merck BioManufacturing Network in the U.K. and an Israeli manufacturer – have both had some batches that failed.

- **SMITH & NEPHEW** rejected a $10.9 billion takeover offer by **Johnson & Johnson** as not high enough.

- **TELEFLEX**, which makes medical and aerospace equipment, bought privately-held **VasoNova**, gaining central venous catheter navigation technology.

NEWS IN BRIEF

ABBOTT's Absorb – first bioresorbable DES approved

Absorb, a bioresorbable coronary stent, received a CE Mark, making it the first approved bioresorbable drug-eluting stent (DES), but the company doesn't plan to launch it immediately. A limited European launch will begin later this year. Abbott is initiating a 500-patient head-to-head trial against Xience Prime as well as a global study (including U.S. sites).

Acetaminophen – new limits on use in combination products

The FDA is limiting the amount of acetaminophen in prescription combination products (especially with opioids) to 325 mg per tablet/capsule to reduce the risk of liver toxicity, and the Agency is requiring a new boxed warning about liver toxicity in the label for all prescription acetaminophen products. The elimination of higher-dose prescription combination acetaminophen products will be phased in over three years. Over-the-counter and IV acetaminophen products are not affected, but several combination opioids under review by the FDA do have too high acetaminophen, and those will be delayed because they will require reformulation before approval.

AstraZeneca

- **Cancer Research UK – signed alliance agreement.** AstraZeneca plans to take combinations of experimental tumor-fighting drugs into early human tests using the charity's medical center network.
- **MedImmune – licensed Amgen's AMG-108.** The monoclonal antibody is being investigated as a treatment for inflammatory conditions. AstraZeneca gets worldwide development rights except in Japan.
- **Zactima (vandetanib) – delayed.** The FDA delayed making a decision on this treatment for inoperable medullary thyroid cancer for an additional three months, from January 7 to April 7, 2011.

Bristol-Myers Squibb

- **Avalide (irbesartan + hydrochlorothiazide) –** Another 65 lots of this antihypertensive medication were pulled from the U.S./Puerto Rican market because of varying levels of irbesartan in the pills. Less than 4 months ago, the company pulled 62 lots of Avalide for the same reason.
- **BMS-790052 (a NS5A inhibitor) and Pharmasset's PSI-7977 (a nucleotide polymerase inhibitor) –** The companies plan to start a trial in hepatitis C combining these two antivirals.

Epilepsy drugs – increase fracture risk in the elderly

Epilepsy medications may increase the risk of bone fractures in the elderly, according to a study published in the ***Archives of Neurology***. Canadian researchers analyzed the medical records of 15,792 people age ≥50 who had non-traumatic fractures between 1996 and 2004 and matched them to 47,289 controls without a fracture. They found the odds ratio for fracture ranged from 1.24 with clonazepam to 1.91 with phenytoin. Of the epilepsy drugs tested, only valproic acid did not significantly increase the fracture risk. The highest risk, not surprisingly, was for patients on more than one epilepsy medication.

KV Pharmaceutical/Hologic's Gestiva (17-alpha hydroxyprogesterone) – delayed again

The FDA delayed for three months making a decision on this drug to prevent premature birth, which was resubmitted to the Agency in July 2010 along with new information requested by the Agency. On January 9, 2011, Hologic gave the FDA even more new data, and the Agency wanted more time to review those data. The new PDUFA date is April 13, 2011. Meanwhile, the FDA has not lifted the hold on shipments of some other products because of manufacturing issues. *Will the company go belly up before the FDA decides on Gestiva?*

Lilly/Alnara Pharmaceuticals' Sollpura (lipro-tamase) – rejected by FDA panel

The FDA's Gastrointestinal Drugs Advisory Committee voted 7 to 4 (with one abstention) that the risk:benefit did ***not*** favor approval of this pancreatic enzyme replacement therapy. Safety wasn't really the issue; the panel just wasn't convinced that, despite the lower pill burden and a lower theoretical viral transmission risk, Sollpura (which the FDA spelled as Solpura, but a company spokesman said is Sollpura) is as effective as the currently approved porcine-derived products, and the panel questioned the clinical meaningfulness of the benefit seen. The committee also asked for more studies, particularly long-term studies and a head-to-head study vs. a porcine product.

Merck

- **Vorapaxar (formerly known as TRA) – one trial stopped, another limited.** A 13,000-patient Phase III trial (TRACER) of this blood thinner in patients with acute coronary syndrome (ACS) was halted. In addition, dosing was halted for a quarter of the patients in another Phase III trial, the 26,500-patient TRA-2P trial of vorapaxar for secondary prevention of heart attacks. In TRA-2P the ~6,000 patients who had a stroke prior to enrollment were discontinued, but the other ~20,500 patients will continue in the study.

  The speculation is that the problem may be excessive bleeding, but the Data and Safety Monitoring Board (DSMB), which recommended the study changes, did not cite a reason, and the company did not elaborate.

- **Parexel International – will collaborate on biosimilars.** The deal focuses on development of a broad range of biosimilar drugs. Parexel will create a new unit dedicated to Merck BioVentures to provide regulatory, strategy, and clinical development resources.

NOVARTIS

- **Biosimilar rituximab –** Novartis announced it will soon start Phase II trials of its own biosimilar of Roche's Rituxan.
- **Gilenya (fingolimod, FTY-720) –** A study by researchers at Scripps Research Institute, published in the ***Proceedings of the National Academy of Sciences***, found an unexpected biological mechanism acting within the central nervous system (CNS) that could enhance the potential of this oral multiple sclerosis drug, making it the first MS drug with direct CNS activity. The method of action of Gilenya is not fully understood, but it was thought to act on the immune system through S1P receptors. But the Scripps researchers believe it has a direct CNS impact, possibly a neuroprotective effect.

SANOFI-AVENTIS

- **Lantus (insulin glargine) – cancer safety still a question.** The FDA still has not decided whether Lantus is associated with an increased cancer risk. The FDA reviewed four 2009 studies (which initially suggested an added cancer risk) as well as a five-year Lantus trial and an ongoing cardiovascular trial but still could not make a definitive decision. However, the company is planning three new epidemiological trials to study the cancer risk further, with results expected in June 2011, and the FDA is discussing a possible review of the Veterans Administration database.
- **Multaq (dronedarone) – liver toxicity.** The FDA said it has received "several" reports of hepatocellular liver injury, including two postmarketing cases of acute liver failure leading to liver transplant, in patients taking Multaq, which is used to treat abnormal heart rhythm in atrial fibrillation (AFib) patients. Both patients previously had normal liver enzymes, but the explanted livers showed evidence of extensive hepatocellular necrosis:
  - ~70-year-old female with AFib who had liver failure after 4.5 months of Multaq.
  - ~70-year-old female with AFib who had liver failure at 6 months.

  The FDA said from July 2009, when Multaq was approved, through October 2010, Multaq prescriptions were dispensed for ~147,000 patients.

  The FDA is adding a warning to the Multaq label about the potential risk of liver injury and is continuing to review Multaq safety. The Agency also is asking doctors to consider measuring liver enzymes periodically, especially during the first six months of treatment, but noted it is unclear whether monitoring can prevent the development of severe liver injury.

REGULATORY NEWS

Biosimilars – no 12-year exclusivity

A bipartisan group of senators sent a letter to FDA commissioner Dr. Margaret Hamburg clarifying that the healthcare law's provision on follow-on biologics means that for 12 years innovator companies will not have to share the underlying data on the innovator biologic – not that another company is prevented from marketing its own similar product during that time. In essence, the senators told the FDA the law does not give the first product 12 years of exclusivity, it just makes it harder for follow-ons to navigate the approval process.

FDA's Sentinel program operational – allows event and claims tracking

The first phase of the FDA's Sentinel program for real-time monitoring of drug safety problems – Mini-Sentinel, a pilot program that accesses patient databases maintained by health plans and other organizations – has gone live. This will allow the FDA to track events and query claims anonymously for 60 million Americans.

Healthcare companies think the FDA's REMS needs major overhauls – first review since 2008

A study by Tufts University Center for the Study of Drug Development (CSDD) found that healthcare companies (drug developers, healthcare providers, insurance companies, etc.) believe the FDA's risk evaluation and mitigation strategy (REMS) program needs a major revision. CSDD said this was the first systematic review of REMS since it was introduced in 2008. ***Drug Store News*** reported that a CSDD official said, "A majority of the organizations…said that a REMS is a poor substitute for other improvements needed systemwide in drug education, communication, use monitoring, patient access, and delivery of care."

- 75% said the program needs an overhaul.
- 68% said REMS programs are a poor substitute for other improvements.
- 86% said risk and benefit information was not well balanced in REMS communications.
- 22% thought REMS was an improvement over the previous risk-management system.

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
	January 2011	
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 25	Consideration of reclassification of **automated external defibrillators** from PMA to 510(k) products	FDA's Circulatory System Devices Advisory Committee
January 26	**Abbott's RX Acculink** carotid stent system	FDA's Circulatory System Devices Advisory Committee
January 26 (approx.)	**Mannkind's Afrezza** (inhaled insulin)	PDUFA date
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
	February 2011	
February 8	Review of **postmarketing studies for cancer drugs** receiving accelerated approval prior to January 1, 2009	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)
	Other future 2011 meetings	
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 8	**Novartis' Arcapta Neohaler** (indacaterol maleate), a QD bronchodilator for long-term use in COPD	FDA's Pulmonary-Allergy Drugs Advisory Committee
March 10	Risk of **neurodegeneration in pediatric patients** from anesthetic drugs	FDA's Anesthetic and Life Support Drugs Advisory Committee
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 7	**AstraZeneca's Zactima** (vandetanib) for inoperable medullary thyroid cancer	**New** 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
April 13	**KV Pharmaceutical/Hologic's Gestiva** (17-alpha hydroxyprogesterone) to prevent premature birth	**New** PDUFA date
June	**King Pharmaceuticals/Pain Therapeutics' Remoxy** (tamper-resistant oxycodone CR) for pain	Approximate PDUFA date
Summer	Report on **FDA 510(k) reform**	Institute of Medicine
October 20	**Johnson & Johnson's abiraterone** for metastatic prostate cancer	PDUFA date