TRENDS-in-MEDICINE

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by Lynne Peterson

Quick Takes

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

Trends-in-Medicine
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SHORT TAKES

- **ALNARA PHARMACEUTICALS' Solpura (liprotamase capsules) –** The FDA's Gastrointestinal Drugs Advisory Committee will review this drug for exocrine pancreatic insufficiency due to cystic fibrosis, chronic pancreatitis, pancreatectomy, etc., on January 12, 2011.

- **AXCAN HOLDINGS**, a privately held drug developer specializing in gastrointestinal conditions, is buying **Eurand NV**, which makes cardiovascular and pain drugs as well as GI drugs.

- **B. BRAUN's addEASE Binary Connector –** The FDA issued a Class I Recall. The addEASE is used to transfer fluid between a partial additive bag (PAB) and a drug vial. The problem is that as addEASE is inserted into a PAB stopper, fragments of the stopper may enter the bag and ultimately get into a patient's body, leading to serious consequences, including pulmonary embolism, stroke, heart attack, and even death. The FDA said Braun PAB containers can continue to be used safely with a standard syringe and needle.

- **CARDINAL HEALTH** bought **Zuellig Pharma China**, probably the largest pharmaceutical importer in China – doing business with ~123,000 pharmacies and 49,000 hospitals and clinics – to expand in the Chinese market, which Cardinal believes will grow 20% annually through 2014.

- **Chinese drug prices –** The Chinese National Development and Reform Commission plans to reduce the price of several drugs, including Roche's antibiotic Rocephin (ceftriaxone) and Bristol-Myers Squibb's cardiac drug Capoten (captopril), by ~19%, effective December 12, 2010.

- **GLAXOSMITHKLINE** (GSK) may purchase a Chinese drug company, **Nanjing MeiRui Pharma**, which has strength in the urology field, to help sell its benign prostate hyperplasia (BPH) drug Avodart (dutasteride) there.

- **HOSPIRA's generic Taxotere (docetaxel) –** The FDA wants a change in the proposed label for this injectable cancer drug before making an approval decision on what could be the first generic Taxotere. Hospira said the labeling issue is related to the concentration. Sanofi-Aventis's Taxotere was originally approved at 10 mg/mL sold in 2 vials. Recently, Sanofi received approval for a single vial of 20 mg/mL. Hospira is seeking approval for a 10 mg/mL concentration.

- **HUMAN GENOME SCIENCES/GSK's Benlysta (belimumab) –** Even though the FDA's Arthritis Advisory Committee recommended approval, the FDA delayed its

decision on what would be the first new treatment for lupus in half a century by three months. The company said that the FDA requested additional information after the advisory committee meeting and that this has been submitted. The new PDUFA date is March 10, 2011.

- **Japanese medical devices** – The Japanese government plans to release new standards for certifying certain Class II (low-risk) medical devices next year in an effort to accelerate the review process, according to Japan's Pharmaceuticals and Medical Devices Agency.

- **JOHNSON & JOHNSON** may seek to renegotiate the terms of its acquisition of Dutch vaccine maker **Crucell** if contamination problems worsen at Crucell's South Korean manufacturing plant, but J&J is still going through with the purchase. Crucell halted shipments of its Quinvaxem vaccine against five childhood diseases and its Hepavax-Gene for hepatitis B because of the contamination.

- **KERYX BIOPHARMACEUTICALS' Zerenex (ferric citrate)** – In a 28-day trial in 151 dialysis patients with hyperphosphatemia, the two highest doses (6 and 8 pills per day) met the primary endpoint, reducing abnormally high phosphate levels in the blood by 25% and 29%, respectively. When a one-year Phase III trial to determine long-term safety is completed, Keryx plans to submit the drug to the FDA.

- **Medical credit cards** – The ***New York Times*** reported that patient advocates and critics of medical credit cards are claiming that many of them use aggressive and misleading marketing tactics.

- **Medicare drug plans** – Increasingly, prescription drug plans competing in the Medicare program are experimenting with new cost-control methods, according to a study by Avalere Health, a healthcare consulting firm. The plans are trying to gain an edge in the Medicare market by negotiating better deals for generic drugs and for specialty drugs included in their formularies. For example, a number of plans have added a fifth tier to their copays.

- **MERCK**
  - Merck is buying **SmartCells**, a biotechnology company that is developing "SmartInsulin," which requires as few as one injection per day.
  - **Isentress (raltegravir)** – A once-daily version of this HIV drug failed in a Phase III trial, not doing as well as the BID version that is already FDA-approved. In the trial, 83.2% of QD patients achieved SVR (undetectable viral levels) at Week 48 vs. 88.9% of BID patients. Merck is recommending that QD patients in the study switch to BID.

- **MERCK KGAA's cladribine** – The FDA extended for three months (to about March 5, 2011) its priority review of this oral treatment for relapsing-remitting multiple sclerosis. Two months ago, Merck failed to get European approval for the drug.

- **NOVARTIS** is reducing its U.S. sales force by 1,400 people, but the cuts reportedly will not affect the cancer sales reps or Sandoz reps.

- **NOVARTIS's Afinitor (everolimus)** – The U.K.'s National Institute for Health and Clinical Excellence (NICE) refused to recommend Afinitor as a second-line therapy for kidney cancer, saying there is "still too much uncertainty" about the drug's cost-effectiveness. Novartis plans to appeal the decision.

- **OCEANA THERAPEUTICS' Solesta** – The FDA's Gastroenterology and Urology Devices Advisory Committee voted 5-0 (with one abstention) that the benefits of this fecal incontinence treatment outweigh the risks in patients who have failed conservative therapy. The panel also voted 6-0 that Solesta, a bulking agent administered as an outpatient series of four 1 mL submucosal injections into the rectum, is safe and 5-1 that it is effective.

- **OCTAPHARMA's Octaplex (freeze-dried human prothrombin complex)**, which is being developed as an antidote to warfarin, was granted fast track status by the FDA. It already has orphan drug status. The ongoing, randomized, open-label, multicenter PROTECT trial is comparing Octaplex to fresh frozen plasma (FFP).

- **OPTIMER PHARMACEUTICALS' fidaxomicin** was submitted to the FDA for the treatment of *Clostridium difficile* (*C. diff*). Optimer is seeking priority review. Fidaxomicin already has FDA fast track designation.

- **Psychiatric drugs** – Nine major pharmas (including Lilly, Pfizer, AstraZeneca, and Roche) have formed a collaboration with major academic centers around the world to create a collective database of the results from 67 clinical trials on 11 approved medications. The goal is to simplify and speed up development of new medicines to treat psychiatric illnesses. The project is called Novel Methods leading to New Medications in Depression and Schizophrenia (NEWMEDS).

- **ROCHE**
  - The company is eliminating 4,800 jobs.
  - **Avastin (bevacizumab)** – In a large study (120 patients) published in the ***International Journal of Radiation Oncology, Biology, Physics***, positive results were reported with Avastin + irinotecan added to

temozolomide-based chemoradiation therapy in patients with newly diagnosed glioblastoma multiforme. The study found the doublet extended both overall survival and progression-free survival (PFS) by ~6 months vs. chemoradiation alone. Yet, critics have complained about the trial design, saying it makes it impossible to determine whether it is the irinotecan or the Avastin – or both – that made the difference.

- **Tarceva (erlotinib)** – NICE rejected Tarceva a second time as a maintenance therapy for non-small cell lung cancer (NSCLC), saying additional evidence is needed before recommending its use.

- **Tricyclic antidepressants** – An 8-year, prospective study published in the ***European Heart Journal*** of 14,784 men and women in Scotland found that tricyclic antidepressants were associated with a 35% increased risk of cardiovascular (CV) disease but that there was no increased risk with selective serotonin reuptake inhibitors (SSRIs).

- **VALEANT PHARMACEUTICALS/GSK'S ezogabine** – The FDA issued a complete response letter, citing "non-clinical" reasons for not approving this medication for adjunctive treatment of adult epileptics with partial-onset seizures. The companies said they believe the issues can be addressed and will respond to the FDA "as soon as possible in 2011." *It sounds like the FDA wants a stronger REMS.*

- **Warfarin** – A ***MedpageToday*** survey found that ~55% of respondents believe that clinicians should ***not*** stop prescribing warfarin in favor of more costly but more convenient alternatives such as Boehringer Ingelheim's Pradaxa (dabigatran) or Johnson & Johnson/Bayer's Xarelto (rivaroxaban).

NEWS IN BRIEF

AMAG PHARMACEUTICALS' Feraheme (ferumoxytol) – label change

AMAG avoided a potentially deadly bullet. The FDA did not require a boxed warning (black box) about hypersensitivity reactions, but the Feraheme label is being updated to mention the risk of serious adverse reactions, including hypersensitivity reactions and significant low blood pressure. In addition, the recommended (read: mandatory) observation period after administration will now be 60 minutes instead of 30 minutes, which is likely to discourage some users. AMAG also is proposing a registry to track Feraheme adverse events.

AMRIN's AMR-101 – lowers triglycerides in pivotal Phase III trial

The results of the MARINE trial showed that AMR-101 (at both 2 g and 4 g) significantly reduced triglycerides vs. placebo, with no significant increase in LDL, and a safety profile comparable to placebo. The company now plans to submit it to the FDA in 2011.

AMR-101 is being developed under a Special Protocol Assessment (SPA) with the FDA as a treatment for very high triglycerides (500 mg/dL), which required the p-value for the primary endpoint – change in triglycerides at Week 12 – be <0.01, and it met that hurdle. The decrease in triglycerides vs. placebo was 33% with 4 g of AMR-101 ($p<0.0001$) and 20% with 2 g of AMR-101 ($p=0.0051$). AMR-101 also demonstrated a positive safety profile.

In a pre-specified secondary analysis in the subgroup of patients with baseline triglycerides >750 mg/dL, AMR-101 reduced triglyceride levels even more (45% with 4 g, 33% with 2 g). In addition, the subgroup of patients on background statin therapy had much greater median reductions in triglycerides than those not on statin therapy.

Amrin claims this is the first and only triglyceride-lowering therapy studied in this population with very high triglyceride levels to show a lack of elevation in LDL. There were no treatment-related serious adverse events in the MARINE study. The company will present more details of these results at an upcoming scientific meeting.

ASTRAZENECA

- **Recentin (cediranib, AZD-2171) – disappointing results.** The results of the Phase III REGAL trial in recurrent glioblastoma were disappointing. Researchers from Massachusetts General Hospital found that this oral VEGF inhibitor ± lomustine (Bristol-Myers Squibb's CeeNU, an alkylating agent) failed to improve progression-free survival, the study's primary endpoint, or overall survival, a secondary endpoint vs. lomustine alone. But other oncologists are not giving up hope for the agent, suggesting higher doses be tested.

- **Vandetanib – approvable but needs more study.** The FDA's Oncologic Drugs Advisory Committee (ODAC) agreed that the benefits of this multitargeted kinase inhibitor outweigh the risks in unresectable locally-advanced or metastatic medullary thyroid cancer (MTC). However, the panel voted 10-0 that, if the FDA does approve vandetanib, postmarketing studies of additional doses should be required to determine the optimal dose. And the panel suggested

that vandetanib be used only in patients who are symptomatic, experiencing pain, problems with swallowing, etc. MTC is a rare cancer, affecting ~4% of all thyroid cancer patients or <1,800 Americans each year. The PDUFA date is January 7, 2011.

FIBROGEN's FG-2216 – positive Phase I results

In an 18-patient Phase I, proof-of-principle study published in the ***Journal of the American Society of Nephrology***, this oral prolyl-hydroxylase inhibitor, which targets hypoxia-inducible transcription factor (HIF), increased natural erythropoietin (EPO) production in dialysis patients as well as in healthy volunteers. In the study, German researchers reported that FG-2216 increased plasma EPO levels from 12.7-fold in healthy volunteers to 30.8-fold in nephric dialysis patients after a single 20 mg/kg dose.

Imaging
– CMS cutting reimbursement for many scans

As part of its final rule for the Hospital Outpatient Prospective Payment System (HOPPS) and Ambulatory Surgical Center (ASC) services, effective January 1, 2011, the Centers for Medicare and Medicaid Services (CMS) will cut overall imaging reimbursement by 0.25%, but the cuts are not even for all imaging procedures. Nuclear imaging will be hardest hit. In addition, some hospitals that did not meet the quality reporting requirements will face a 2% reduction. Comments must be submitted to CMS by January 3, 2011, and the American Society of Nuclear Cardiology said it plans to submit comments.

Key Changes in CMS 2011 Reimbursement for Imaging

Procedure	New rate	Old rate	Change
MRI and SPECT	$ 768.38	$ 773.20	– 1%
PET heart muscle image	$ 1,099.16	$ 1,429.36	– 23%
Cardiac CT without dye	$ 47.10	$ 45.00	+ 5%
Cardiac CT with 3-D image	$ 258.02	$ 224.19	+ 15%
Cardiac CT with 3-D image, congenital	$ 258.02	$ 325.22	– 21%
Cardiac CT angiography with 3-D image	$ 258.02	$ 268.49	– 4%
Cardiovascular stress test	$ 179.55	$ 175.74	+ 2%

Isotretinoin
– dermatologists say benefits still outweigh the risks

The American Academy of Dermatology (AAD) issued a position statement defending the use of isotretinoin for severe acne despite evidence that suggests it is associated with an increased risk for suicide and inflammatory bowel disease (IBD). The AAD said the evidence is not strong enough for physicians to stop prescribing the drug and pointed out that psychiatric studies of isotretinoin patients have also found mental health benefits.

As for IBD, the AAD statement said, "Current evidence is insufficient to prove either an association or a causal relationship between isotretinoin use and IBD in the general population…Further studies are required to conclusively determine if the association or causal relationship exists and/or whether IBD risk may be linked to the presence of severe acne itself."

The AAD statement also supported off-label use of isotretinoin for cornification (e.g., corns on the hands or feet) and chemoprevention of skin cancer in high-risk patients, with informed patient consent.

Roche's Accutane, the first FDA-approved isotretinoin, was withdrawn from the U.S. market in 2009, but several generic versions are available.

The AAD conclusion was: "The prescription of isotretinoin for severe nodular acne continues to be appropriate as long as prescribing physicians are aware of the issues related to isotretinoin use, including IBD or psychiatric disturbance, and educate their patients about these and other potential risks. Physicians also should monitor their patients for any indication of IBD and depressive symptoms."

JOHNSON & JOHNSON
– the manufacturing problems – and the recalls – keep mounting

Problems with the manufacturing plant in Puerto Rico continue to escalate. Most recently, FDA inspectors reported that J&J subsidiary McNeil Consumer Healthcare failed to correct flaws at the plant that were cited in a warning letter earlier this year. In the latest Form 483, the FDA said J&J "continues to have serious quality control issues at its plant and that it is not in compliance with current good manufacturing practices required by federal law."

The FDA cited a variety of problems, including:

- Distribution of drugs that failed quality requirements.
- A failure to identify product defects during routine testing.
- Failure to detect incorrect expiration dates on drug labels.
- Failure to adequately investigate product problems.
- Failure to follow laboratory controls and inadequate training of lab staff.

J&J obviously didn't learn from GlaxoSmithKline. GSK also had problems with its plant in Puerto Rico. The FDA seized drugs and basically shut down the plant, but GSK got it resolved relatively quickly by bringing in top-flight outside quality assurance experts. The chance of an FDA enforcement action against J&J is looking more, not less, likely.

On top of this, J&J announced a new recall. This time it was 12.3 million bottles of Mylanta in the U.S. and Puerto Rico plus 84,750 bottles of AlternaGel, a heartburn medicine, because the labels failed to mention the alcohol content of the products, which were made at the company's Lancaster PA plant.

ORBUSNEICH's Genous Stent – positive results in bifurcations

One-year trial data from a single-center study of 178 consecutive Genous patients vs. 465 consecutive bare metal stent (BMS) patients were reported in the journal ***Atherosclerosis***. In the study, this endothelial progenitor cell capture stent met the primary endpoint, reducing the composite of cardiac death, MI, or target lesion revascularization (TLR) by 30% (12.4% vs. 17.2% for the bare metal stent control) in patients with *de novo* bifurcation lesions. Definite/probable stent thrombosis was 1.7% for Genous vs. 3.4% for bare metal stent.

Prostate cancer

- **No prevention label for BPH drugs –** The FDA's Oncologic Drugs Advisory Committee rejected new indications or labels for two drugs already approved to treat benign prostate hyperplasia (BPH):
  - **Merck's Proscar (finasteride) –** ODAC recommended this drug not be approved to prevent prostate cancer, saying it could actually raise the risk of the most serious types of tumors.
  - **GlaxoSmithKline's Avodart (dutasteride) –** ODAC recommended against changing the label to say that it could reduce a man's risk of getting prostate cancer.

  Dr. Richard Pazdur, director of the FDA's Office of Oncology Drug Products, said the FDA must have "a very high level of certainty" before granting a prevention label because that would lead to a drug being prescribed to "relatively healthy men…men who don't have disease."

- **Possible new therapeutic approach –** According to an article published in ***Nature Medicine***, monoclonal antibodies specific to the protein N-cadherin may delay prostate cancer metastasis and progression to castration resistance. The UCLA researchers studied prostate cancer cell cultures, mice transplanted with androgen-dependent and castration-resistant prostate cancer (CRPC) cells, and tissue samples obtained from men who died from prostate cancer. They eventually developed two monoclonal antibodies against N-cadherin, which slowed invasion, attachment, and proliferation in CRPC cell lines as well as in mouse models of CRPC, and the monoclonal antibodies delayed the time to castration resistance. (*For more information, see* **www.nature.com/nm/journal/vaop/ncurrent/abs/nm.2236.html**)

REGULATORY NEWS

FDA gets mixed reviews in survey

PricewaterhouseCoopers, in conjunction with Biocom and the Massachusetts Biotechnology Council, surveyed 1,000 adults and 50 life science company executives and found that:

- 93% of consumers are confident about the safety and efficacy of drugs that the FDA already has approved.
- Industry executives:
  - Believe their relationship with the FDA has improved.
  - Are increasingly concerned about the approval process and the FDA's ability to keep up with the pace of scientific and technological innovation.
  - Are not happy with the prospect of an FDA path for biosimilar versions of biotech drugs or proposals to make comparative effectiveness research a criterion in the FDA approval process.
  - Only 8% feel the FDA is working to spur personalized medicine.
  - 78% praised FDA guidance documents.
  - 68% said they themselves have done a better job of incorporating feedback from regulators.
  - >60% said the FDA changed its position during at least one review, and 56% said the regulatory approval process lags behind scientific and technological advances.

Is FDA getting all non-U.S. trial data?

According to an article in ***Vanity Fair***, 6,485 clinical trials were conducted overseas in 2008 on drugs intended for American use vs. 271 in 1990. Does the FDA see all of these? Maybe not. An FDA spokesperson admitted that some clinical trials are done overseas without being submitted to the Agency, but she added that all Phase II and III trials have to be submitted with a New Drug Application (NDA).

PDUFA reauthorization

Tevi Troy, former deputy secretary of the department of Health and Human Services (HHS), urged Congress to listen to industry criticisms of the FDA when working on legislation to reauthorize the Prescription Drug User Fee Act (PDUFA) next year.

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 7	**Orexigen Therapeutics' Contrave** (naltrexone + bupropion), a diet drug	FDA's Endocrinologic and Metabolic Drugs Advisory Committee
December 8	Appropriate clinical **study design for thromboxane receptor antagonists for prevention of cardiovascular events** (e.g., MI) in patients with aspirin intolerance due to immunologically-based adverse reactions, specifically in the setting of CABG	FDA's Cardiovascular and Renal Drugs Advisory Committee
December 14-15	Risk of dengue virus infection in blood donors, murine leukemia virus-related human retroviruses, and an update on **blood safety issues**	FDA's Blood Products Advisory Committee
December 15-16	**Automated external defibrillator** safety and development	FDA public hearing
December 16	**AstraZeneca's Brilinta** (ticagrelor), an anticoagulant	PDUFA date
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 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	
March 5 (about)	**Merck KGaA's cladribine** for multiple sclerosis	**New 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	**New PDUFA date**
March 26	**Bristol-Myers Squibb's Yervoy** (ipilimumab) for advanced melanoma	PDUFA date
Date TBA	Review of **accelerated drug approval process**	FDA's Oncologic Drugs Advisory Committee (ODAC)
Summer	Report on **FDA 510(k) reform**	Institute of Medicine