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

- **AETNA** announced that it will acquire **Medcity**, a provider of health information exchange services.
- **Alzheimer's disease –** Research reported in ***Science*** suggests that the root case of Alzheimer's disease (AD) may be the brain's inability to get rid of amyloid-beta protein rather than over-production of amyloid beta. In comparing the brains of patients with late-onset Alzheimer's and health controls, the researchers found that beta-amyloid production rates were nearly identical in the two groups, but clearance rates were 30% lower in AD patients.
- **ARTERIAL REMODELING TECHNOLOGIES' (ART's) bioresorbable stent –** French researchers reported data at the Innovations in Cardiovascular Interventions (ICI) meeting in Tel Aviv, Israel, indicating that this bioresorbable PLA (polylactic acid) coronary stent can be overinflated by more than 25% without cracking or crazing. Thus, ART's stent reportedly avoids the malapposition that has been associated with other bioresorbable stents.
- **AVID RADIOPHARMACEUTICALS' florbetapir F-18 injection**, for use in positron emission tomography (PET) imaging of ß-amyloid (beta-amyloid) aggregates in the brain to help rule out Alzheimer's disease, will be reviewed on January 20, 2011, by the FDA's Peripheral and Central Nervous System Drugs Advisory Committee. *Remember Lilly is acquiring Avid.*
- **BAYER's gadobutrol injection –** The FDA's Peripheral and Central Nervous System Drugs Advisory Committee will review this MRI contrast agent for imaging disruption in the blood brain barrier and/or abnormal vascularity of the central nervous system on January 21, 2011.
- **BRISTOL-MYERS SQUIBB's Yervoy (ipilimumab) –** The FDA has rescheduled the Oncologic Drugs Advisory Committee meeting on this treatment for advanced melanoma for February 9, 2011. It was originally scheduled to be reviewed on December 2, 2010. The FDA PDUFA date is March 26, 2011.
- **COMMUNITY HEALTH SYSTEMS** is trying to buy rival hospital operator **Tenet Healthcare**, asking shareholders to override the Tenet board of directors, which rejected Community's offer. A combined company would own or operate 176 hospitals in 30 states.
- **COMPUGEN** has signed a research collaboration agreement with **Seattle Genetics** for a Compugen-discovered oncology target. Under the agreement, Seattle Genetics has an exclusive research license to evaluate monoclonal antibodies and antibody-drug

conjugates aimed at Compugen's solid tumor target, and it has an option for exclusive commercial licensure.

- **Drug Enforcement Administration (DEA)** – According to a report in ***The Hill's Healthwatch*** blog, Senate approval of President Obama's nominee to head the DEA, Michele Leonhart, is being held up over a demand by Sen. Herb Kohl (D-WI) that nurses be allowed to write prescriptions for – and administer – narcotics such as morphine to nursing home patients when a doctor is unavailable.

- **e-cigarettes** – The U.S. Court of Appeals for the District of Columbia said the FDA cannot prove electronic cigarettes are harmful, and the court ruled that the FDA cannot regulate the battery-operated cigarette look-alikes as a drug or as a device provided the manufacturer (Njoy) doesn't market them as a smoking cessation aid. Njoy says its device is for "smoking pleasure," not smoking cessation.

- **JOHNSON & JOHNSON/MCNEIL CONSUMER HEALTHCARE** is recalling another over-the-counter product. This time it is 13 million packages of Rolaids after bits of wood or metal were found in the tablets. J&J said the problem may have stemmed from a third-party manufacturer, and it is suspending production of Rolaids until the issue is resolved.

- **MEDTRONIC's Activa** – The U.S. Attorney's office in New York issued a subpoena to Medtronic seeking information about its marketing and reimbursement of these implantable deep-brain stimulation devices.

- **MERRION PHARMACEUTICALS** signed a deal with a large, unnamed big pharma to use its oral drug delivery technology, GIPET, to boost the bioavailability of three of the pharma's compounds, which have varying molecular weights. If feasibility studies are successful, the pharma has the option to license the GIPET technology.

- **OREXIGEN THERAPEUTICS' Contrave (naltrexone + bupropion)** – The FDA's Endocrinologic and Metabolic Drugs Advisory Committee voted 13-7 that the benefits of this fixed-dose diet drug outweigh its risk. The panel was split on whether a larger safety study should be done before (8 votes) or after (11 votes) approval.

- **PENUMBRA's Penumbra System Reperfusion Catheters** – The FDA issued a Class I recall of this stroke therapy device due to a manufacturing error that resulted in mid-shaft joint failures.

- **PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA (PhRMA)** – Christopher Viehbacher, Sanofi-Aventis CEO, is the new chairman of the board of PhRMA, replacing Jeffrey Kindler, who suddenly resigned as president/CEO of Pfizer.

- **Prostate cancer** – The U.K.'s National Screening Committee recommended against routine PSA screening, but men who ask for it will be allowed to have the test. The committee determined that the potential risks of testing – worry, anxiety, unneeded additional testing – outweigh the potential benefits and that a better prognostic test is needed. The policy will be reviewed in three years.

- **QR PHARMA's bisnorcymserine** – The FDA gave the company permission to begin a trial of bisnorcymserine, which was discovered by a National Institutes of Health (NIH) researcher, to improve cognition in later-stage Alzheimer's disease patients.

- **ROCHE's RG-1678** –The company reported positive results with this experimental schizophrenia drug, saying it reduced symptoms and produced beneficial changes in patients' personal and social functioning. RG-1678 is a first-in-class glycine reuptake inhibitor that impacts the negative symptoms of schizophrenia, such as apathy, lack of emotion, non-existence/poor social functioning. In contrast, the atypical antipsychotics affect positive symptoms, such as hallucinations.

- **SANOFI-AVENTIS's Emerflu (H5N1)** – The company withdrew its European application to market this pandemic influenza vaccine.

NEWS IN BRIEF

ABIOMED's Impella – failed to beat IABP

The PROTECT-II trial of this percutaneous hemodynamic support device vs. intra-aortic balloon pump (IABP) was stopped early after a planned interim analysis determined it was futile to continue. The primary endpoint – MACE at 30 days – was 32% for Impella vs. 43% for IABP (p=0.11). The failure to show a MACE benefit was blamed on more frequent use of rotational atherectomy in the Impella arm. The full results will be presented at the American College of Cardiology meeting in March 2011.

However, the FDA gave Abiomed conditional permission to begin the prospective, randomized, five-site, 50-patient MINI-AMI trial of Impella 2.5 used for 24 hours post-PCI to reduce infarct size in STEMI patients. This pilot study will determine if Impella can shrink infarct size. The primary endpoint will be a cardiac MRI-assessed ratio of the final infarct area to the total myocardial area at risk, measured 3-5 days after treatment and then again at 90 days.

ALLERGAN

- **Lap-Band – approval may be expanded.** The FDA's Gastroenterology and Urology Devices Advisory Committee voted 8-2 to recommend that Lap-Band use be expanded to include less obese patients, those with a body mass index (BMI) as low as 30 for patients who also have at least one comorbid condition, and 35 for those who don't.
- **Lumigan (bimatoprost) – advertising steps over the line.** The FDA sent the company a warning letter, saying a direct mail advertisement was false or misleading because it made "unsubstantiated superiority claims" over Pfizer's Xalatan (latanoprost). The FDA said the marketing materials "misleadingly imply that treatment with Lumigan is superior to treatment with latanoprost in that Lumigan will be effective after latanoprost stops working or when latanoprost is no longer effective in adequately lowering intraocular pressure (IOP), when this has not been demonstrated by substantial evidence or substantial clinical experience."

ASTRAZENECA

- **Under investigation.** The European Commission raided the offices of AstraZeneca and other unnamed pharmas in an investigation into whether the companies acted, individually or collaboratively, to keep lower-priced generics off the market.
- **Brilinta (ticagrelor) – gets European approval.** European regulators approved this blood thinner, which will be sold in Europe as Brilique, for acute coronary syndrome in adults, and AstraZeneca expects to begin selling it in most EU countries in 2011. The FDA's decision (PDUFA) date is December 16, 2010.

Computerized provider order entry (CPOE) – challenge for hospitals

According to a survey conducted in November 2010 by the College of Health Information Management Executives (CHIME), implementation of CPOE is looming as one of the more difficult objectives for hospitals to achieve, with more than half of chief information officers (CIOs) identifying CPOE as a challenge. The situation appears to have worsened since a CHIME survey in August 2010.

- CIOs are far less confident about CPOE implementation than they were a few months ago. Now, only 5% expect to qualify for federal stimulus funds under the HITECH portion of the American Recovery and Reinvestment Act (ARRA) in the first six months of the program vs. 23% who previously said they expected to qualify.
- 15% now expect to qualify for stimulus funding in the first six months of fiscal year 2011 (which began on October 1, 2010) vs. 28% who expected to qualify for funding by April 1, 2011.
- The biggest issue in CPOE adoption is getting clinical staff to use the systems.
- 42% expect to accelerate electronic health record (EHR) implementation plans, nearly double the 24% who responded similarly in the previous survey.
- Only 32% of CIOs now believe their organizations are well positioned to qualify for funding vs. 48% in the previous survey.
- In both surveys, only ~10% believe their hospital will ***not*** qualify for stimulus funds until fiscal years 2013 or 2014.
- 82% continue to have concerns about meeting meaningful use objectives and qualifying for stimulus funding, but the nature of those concerns has shifted dramatically:
  - CIOs now report fewer uncertainties when it comes to EHR certification.
  - Implementation of CPOE, capturing/submitting quality measures, and vendor readiness are now larger concerns.

Congress – Republicans bring shift in pharma oversight

In an interview with the ***Wall Street Journal***, Rep. Darrell Issa (R-CA), who is scheduled to become chairman of the House Oversight and Government Reform Committee, expressed some ideas that may have significant impact on healthcare in the U.S. Some of those messages were:

- One of his top priorities will be cutting medical costs, and his focus appears to be on medical devices, particularly cardiovascular and orthopedic implants (he mentioned spinal implants specifically).
- He supports comparative effectiveness research, conducted by medical professionals not bureaucrats.
- The FDA has been overreacting to some outbreaks of food-borne illnesses linked to eggs and produce.

Growth hormone – safety in question

The European Medicines Agency (EMA) is conducting a safety review of somatotropin (recombinant analogs of human growth hormone) products after a new study suggested increased mortality long term, especially at higher-than-recommended doses. The EMA plans to "look into all available data on somatropin to reassess the benefit:risk balance of these medicines."

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. *Will the FDA follow suit and do its own investigation?*

Healthcare reform – unintended consequences

Pharmas are informing children's hospitals that they are ending discounts on orphan drugs because of a change mandated by the health reform law. Children's hospitals are hopeful that Congress will pass a new bill to restore the discounts.

ROCHE's Avastin (bevacizumab) – earlier is not better in glioblastoma

Avastin failed to prolong survival in a trial of newly diagnosed glioblastoma patients when added to radiotherapy plus Merck's Temodar (temozolomide). In results published in the ***Journal of Clinical Oncology***, overall survival was 21.1 months with radiotherapy/Temodar vs. 19.6 months when Avastin was added. Avastin already has accelerated approval for advanced/ refractory glioblastoma.

ROCHE/HALOZYME THERAPEUTICS' Herceptin SC (trastuzumab subcutaneous) – something to watch

The companies announced completion of enrollment in a pivotal, multicenter, randomized, open-label, non-inferiority, 595-patient Phase III trial comparing IV Herceptin and this subcutaneous formulation using Halozyme's Enhanze technology (rHuPH20, recombinant human hyaluronidase) in women with early stage HER2-positive breast cancer. The two primary endpoints are: (a) complete pathological response between treatment cycles 8 and 9 and (b) serum concentration during the first 8 cycles.

Russian message to global pharmas – invest locally or else

In remarks made at a Russian Cabinet meeting and posted on the government's website, Russian Prime Minister Vladimir Putin warned that his government will implement restrictions on access to the Russian market if global pharmas and device makers do not establish production in – and transfer technology to – his country. He compared the healthcare sector to the auto industry, where Russia forced automakers to step up Russian production by using a combination of higher import duties and consumer incentives.

Putin accused foreign firms of exaggerating health benefits when marketing their imported products in Russia, "Foreign producers with the help of some of our celebrities are pushing their products, saying that without them everyone will die. We just need to get over it."

The Russian government also plans to make a $3.8 billion investment by 2020 to boost the pharmaceutical sector. Some pharmas already are responding. Nycomed and Novo Nordisk announced plans to start production in Russia, and AstraZeneca and Novartis reportedly are considering it.

San Antonio Breast Cancer Symposium – early highlights

- **Aromatase inhibitors – may increase CV risk.** A meta-analysis of seven large clinical trials suggests that the relative risk of a cardiovascular (CV) event is increased 26% ($p \leq 0.01$) with an aromatase inhibitor, but the absolute increase was small (3.4% to 4.2%). And the excess risk was reduced if a woman takes tamoxifen first and then switches to an aromatase inhibitor. Women in the study also had a 47% increased risk of a bone fracture. However, women taking an aromatase inhibitor had fewer venous thromboembolic events and less endometrial cancer.

- **Breast cancer screening rates – many women not getting mammograms.** A Medco Health Solutions study found:
  - Only 50% of women age ≥40 with insurance coverage get an annual mammogram.
  - 60% of women age ≥40 had ≥2 mammograms over four years.
  - The average rate of annual mammography varied little by age group: 47% of women in their 40s, 54% of those 50-64, and 45% of women ≥age 65.
  - 77% of women had received at least one mammogram in four years.
  - Reasons for not getting a mammogram included: cost, discomfort, and fear.

- **NOVARTIS's Zometa (zoledronic acid IV) – not helpful in early stage breast cancer.** Zometa did not meet the primary endpoint in the five-year, 3,360-patient AZURE trial, failing to improve disease-free survival (DFS) in women with early (Stage II/III) breast cancer. The researchers warned that clinicians now should be cautious about using Zometa in the adjuvant setting in **premenopausal** women. Dr. Robert Coleman, a U.K. oncologist and the principal investigator, said, "This will likely dissuade clinicians from giving adjuvant bisphosphonates on a routine

basis to younger women taking adjuvant chemotherapy because, although the drug is generally well tolerated, there is a small risk of osteonecrosis of the jaw."

In **postmenopausal** women, there was a 29% improvement in overall survival. The researchers said that secondary finding will need further study. Dr. Coleman said, "To see a survival advantage like this is quite remarkable, and the difference in outcome between this group and the younger population is unlikely to be a chance finding. We will clearly want to investigate further in this population."

However, these results should not impact the current usage of Zometa for the treatment of metastatic bone disease in a wide range of cancers. And it doesn't impact the approval or use for osteoporosis, where it is sold as Reclast.

Novartis plans to withdraw applications in the U.S. and Europe to expand Zometa approval to prevent breast cancer relapse beyond its current approval as a treatment for patients whose cancer has spread to the bone.

- **ROCHE's Herceptin (trastuzumab) – beneficial addition to early breast cancer therapy.** Adding Herceptin to pertuzumab (Roche's Omnitarg) + chemotherapy (docetaxel) significantly improved the rate of complete tumor disappearance in the Phase II NEOSPHERE trial in women with newly diagnosed, early-stage HER2-positive breast cancer (pCR 45.8% vs. 29.0% with Herceptin + chemo, p=0.014). The benefits were achieved without a significant increase in side effects or cardiac risk. Roche now plans to start a Phase III study in HER2-positive early (adjuvant) breast cancer in 2011. The ongoing CLEOPATRA trial of the combination as first-line therapy in HER2-positive metastatic breast cancer patients completed enrollment in 2Q10, and results are expected by the end of 2011.

Spine surgery – BC/BS tightens policy on lumbar fusion

The International Society for the Advancement of Spine Surgery (SAS) sent an alert to its members on November 17, 2010, advising them that North Carolina Blue Cross/Blue Shield is implementing a more restrictive policy for lumbar fusion, effective January 1, 2011. The alert called the new policy overly restrictive and warned that it may negatively affect patient access and could lead to "a grave international issue."

SAS normally sticks to scientific issues, but ***Orthopedics This Week*** reported that the society wants to be "more proactive on such access questions and sees the society increasing its influence and working with other surgical societies to better represent the interests of patients and surgeons."

SAS cited "several common scenarios where the standard of care includes fusion; however, this more restrictive policy may make it more difficult for those patients suffering low back pain due to spondylolisthesis to receive needed surgeries." These scenarios include:

- Patients with degenerative spondylolisthesis who have more back pain than leg pain.
- Patients with isthmic spondylolisthesis that is not progressive but painful.
- Patients where fusion for spondylolysis may be necessary/beneficial in situations where there is no slip and only back pain.
- Patients where fusion is the only procedure that will relieve pain and immobility associated with degenerative disc disease, after six months of exhaustive conservative measures have failed.

The BC/BS policy is available at:
www.bcbsnc.com/assets/services/public/pdfs/medicalpolicy/lumbar_spine_fusion_surgery.notification.pdf

REGULATORY NEWS

FDA urged to be cautious with 510(k) reform – senators question impact on innovation

Fifteen senators wrote FDA Commissioner Dr. Margaret Hamburg urging her to exercise more caution before implementing proposed changes to the 510(k) process. The senators are worried about the impact of the changes on innovation.

The letter included this:

> *Given the potential for enormous disruption in the innovation process, we believe FDA must proceed cautiously. We believe FDA should focus first on non-controversial proposals, but before any proposed to the 510(k) is implemented, it is essential that FDA provide stakeholders ample notice and opportunity for comment.*
>
> *In addition, we believe FDA must operate in a transparent fashion and provide greater detail on the specifics of each proposal before moving forward. And FDA should carefully consider the impact of any proposed change on the ability of*

companies to innovate in a predictable and consistent regulatory environment so they can continue to bring medical advances to patients.

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 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 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)
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
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