TRENDS-in-MEDICINE

December 19, 2010

by Lynne Peterson and D. Woods

Quick Takes

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

SHORT TAKES

- **ACETO**, which provides sourcing, quality assurance, regulatory support, marketing, and distribution of pharmaceuticals, nutraceuticals, and specialty chemicals, is buying certain assets of **Rising Pharmaceuticals**, which markets and distributes generic prescription and over-the-counter pharmaceutical products to wholesalers, chain drugstores, distributors, mass market merchandisers, etc.

- **AMGEN's Xgeva (denosumab)** significantly delayed the spread of prostate cancer to the bone in Study 147, but it did not affect overall survival in men with castrate-resistant prostate cancer (CRPC). The 1,432-man study found Xgeva extended bone metastasis-free survival by 4.2 months vs. placebo, and it significantly improved the time to first occurrence of bone metastases.

- **CORNERSTONE HEALTHCARE GROUP and SOLARA HEALTHCARE**, two Texas-based long-term acute care hospital firms, have merged, giving them a total of 18 facilities in Texas, Louisiana, Arizona, West Virginia, Ohio, and Oklahoma.

- **Healthcare reform –** Virginia federal district judge Henry Hudson ruled the provision in the Affordable Care Act (ACA) that requires individuals to buy health insurance is unconstitutional, but he did not invalidate the entire healthcare reform law. The legality of the insurance provision, which doesn't take effect until 2014 anyway, will be up in the air until the Supreme Court eventually rules.

- **HIV drugs –** Tight economic times have led some states to cut back on programs that provide free HIV drugs. According to a ***Business Week*** story, at least 19 states have taken steps such as capping enrollment, dropping patients, instituting waiting lists, lowering the income ceiling for eligibility, and no longer covering certain drugs or tests. Advocates say >4,500 people are on waiting lists and hundreds have been dropped from programs because of lower income limits.

- **INTERCELL** has stopped development of its needleless vaccine patch to prevent travelers' diarrhea after it failed in two studies of 2,759 travelers from Europe to Mexico, Guatemala, and India.

- **JOHNSON & JOHNSON –** First, it was manufacturing problems in Puerto Rico. Now, FDA inspectors have found quality flaws in manufacturing at the company's McNeil Consumer Healthcare plant in Pennsylvania. The FDA inspectors found the company didn't properly address customer complaints or thoroughly review unexplained discrepancies relating to the over-the-counter products made there. *Stronger FDA action is getting more and more likely because the situation just does not seem to be improving.*

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- **LILLY's tasisulam** – A Phase III trial in refractory metastatic melanoma was stopped by the company, so it can review "safety concerns" that arose in the study. Studies are continuing in soft tissue sarcoma as well as breast, ovarian, and renal cancers.
- **MERCK KGAA** is replacing its head of pharmaceuticals, Elmar Schnee, blaming him for the regulatory problems with the oral multiple sclerosis drug cladribine, among other things.
- **MIRACOR's PICSO Impulse System**, a pressure-controlled intermittent coronary sinus occlusion device to improve microcirculatory blood flow, received a CE Mark. The company plans to initiate the RAMSES trial in 2011 at seven European sites, using PICSO in acute coronary syndrome patients.
- **MOLECULAR INSIGHT PHARMACEUTICALS** is filing for Chapter 11 bankruptcy protection.
- **National Cancer Institute's Clinical Trials Cooperative Groups** are being consolidated from 10 groups to no more than four adult groups and one pediatric group. The NCI said the change is being made because "oncology has begun to evolve into a more molecularly-based discipline, including genetic subclassification of tumors and individualized treatments" and this will help prepare for "an era of complex, multidisciplinary cancer trials."
- **NOVARTIS** is taking full control of **Alcon**, buying the rest of the stock that it doesn't already own and ending an 11-month dispute with minority shareholders.
- **NOVAVAX's respiratory syncytial virus vaccine** – The company got permission from the FDA to go ahead with a Phase I study of this vaccine. The FDA had put the vaccine on hold in November 2010, asking for additional data on the chemistry, manufacturing, and controls.
- **NYMOX PHARMACEUTICAL's NX-1207** – The company signed a European licensing agreement for development and commercialization with this potential treatment for benign prostatic hyperplasia (BPH) with **Recordati**. NX-1207 is currently in Phase III development.
- **ST. JUDE MEDICAL's Riata ICD lead** – The company notified physicians that it started phasing out Riata and Riata ST defibrillator leads because they have a 0.47% "insulation abrasion" rate over nine years, which could cause the defibrillators to malfunction, but the company insisted this is not a recall. St. Jude already introduced newer leads that mostly replaced Riata.
- **SAMSUNG ELECTRONICS** acquired a controlling stake in **Medison**, a South Korean medical equipment manufacturer of ultrasound monitors. Samsung is diversifying away from consumer electronics and reportedly plans to spend billions of dollars over the next 10 years to enter higher-margin industries such as medical products and solar equipment.
- **SANOFI-AVENTIS SA and MERCK KGAA** will jointly study experimental cancer treatments, particularly Phase I trials of Merck's MSC-1936369B and Sanofi's SAR-245409 and SAR-245408. Sanofi also will be granted a license to study the combination of MSC-1936369B and SAR-245408.
- **SCICLONE PHARMACEUTICALS' SCV-07** missed the primary endpoint in a Phase IIb trial in hepatitis C, and the program is being cancelled. The company plans to start another Phase IIb study in 2011 in oral mucositis using a higher dose.
- **STERIS** got a warning letter from the FDA, saying that the company failed to keep proper records and perform adequate quality control at its contract sterilization facility in Grand Prairie, Texas.
- **VIVUS's Qnexa (phentermine + topiramate)** – The company submitted documents to the FDA in answer to the complete response letter the FDA issued in October 2010 asking for more information on heart risk, etc. Vivus plans to meet with the FDA's Endocrinologic and Metabolic Drugs Division in late January to discuss a proposed refiling.

NEWS IN BRIEF

AstraZeneca's Brilinta (ticagrelor) – fails to get FDA approval

After taking an extra three months to make a decision on this blood thinner that would compete with Sanofi-Aventis's Plavix (clopidogrel) – and despite a positive recommendation from the Cardiovascular and Renal Drugs Advisory Committee – the FDA did not approve Brilinta, instead issuing a complete response letter. The company said the FDA asked for additional analysis of the pivotal PLATO trial of Brilinta vs. Plavix, but an investigator said he couldn't see what more could be learned from that data, which has been carefully analyzed already. Is the issue bleeding, or the lack of a benefit in North American patients? *Despite what AstraZeneca said, it sounds like a trial in U.S. patients may be necessary.*

BRISTOL-MYERS SQUIBB's Yervoy (ipilimumab) – may work in NSCLC as well as melanoma

In a 204-patient Phase II study reported at the Chicago Multidisciplinary Symposium in Thoracic Oncology, this anti-

CTLA-4 monoclonal antibody, when used either concurrently or phased with paclitaxel and carboplatin, improved immune-related progression-free survival (PFS) better than chemo-therapy alone as first-line treatment for Stage IIIb/IV non-small cell lung cancer (NSCLC). PFS was 5.68 months with the phased therapy (p=0.026), 5.52 months with concurrent therapy (p=0.094), and 4.63 months with chemo alone. In this study p=0.1 was significant. Researchers said the findings were sufficient to warrant a Phase III trial, but there is no timetable for that yet.

The primary endpoint of immune-related progression-free survival was chosen because in melanoma, the response to Yervoy was occasionally accompanied initially by tumor growth before shrinkage or by the development of small new lesions, and this endpoint permitted patients to stay in the trial if those occurred. It is not clear what endpoint the FDA will require for Phase III, but an overall survival benefit may be necessary.

Carotid artery stenting (CAS) – riskier than carotid endarterectomy (CEA)

A retrospective study by researchers from Beth Israel Deaconess Medical Center, published in the ***Journal of Vascular Surgery***, looked at 56,564 CAS patients and 482,394 CEA patients, comparing the composite of postoperative death, stroke, and combined stroke or death, stratified by high-risk vs. non-high-risk status and symptom status. They found:

- In both high- and low-risk patients, mortality was higher after CAS than CEA.
- Multivariate predictors of combined stroke or death adjusted for age and gender included:
  - CAS vs. CEA (odds ratio 2.4)
  - symptom status (OR 6.8)
  - high risk (OR 1.6)
  - earlier year of procedure (OR 1.1)
- Stroke was higher in both risk groups after CAS.

Comparison of CAS and CEA

Measurement	CAS	CEA
Symptomatic	13.1%	9.4%
CABG and/or valve repair	2.8%	4.0%
Primary endpoint: Composite of postop death, stroke, and combined stroke or death	8.1%	12.3%
Combined stroke or death in patients undergoing CABG/V during same admission	4.8%	3.2%
High-risk patients		
Combined stroke or death in **asymptomatic** patients	1.5%	1.2%
Combined stroke or death in **symptomatic** patients	14.4%	6.9%
Non-high-risk patients		
Combined stroke or death in **asymptomatic** patients	1.8%	0.6%
Combined stroke or death in **symptomatic** patients	11.8%	4.9%

Healthcare IT – Epic gets top rating by KLAS

In the 2010 Best in KLAS annual ranking of healthcare IT vendors, based on 17,000 interviews, Epic ranked top overall with a score of 87.0 (out of 100), with Picis and Philips taking second and third place, respectively.

KLAS Best Software Vendors

Category	Best vendor
Acute Care EMR	Epic
Ambulatory EMR >100 physicians	Epic
Ambulatory EMR 26-100 physicians	eClinicalWorks
Ambulatory EMR 6-25 physicians	Greenway Medical
Ambulatory EMR 2-5 physicians	e-MDs
Application hosting	Cerner
Financial ERP	McKesson (Pathways)
Community hospital information system	McKesson (Paragon)
Decision support – business	Allscripts (Sunrise)
Pharmacy	Epic
Practice Management >100 physicians	Epic
Practice Management 26-100 physicians	McKesson (Horizon)
Practice Management 6-25 physicians	Greenway Medical
Practice Management 2-5 physicians	e-MDs
Radiology	Epic

INSPIRE PHARMACEUTICALS' denufosol – positive data in cystic fibrosis published

Cystic fibrosis (CF) patients with normal to mildly impaired lung function may benefit from denufosol, an ion channel blocker, according to researchers who published the findings from the 352-patient, Phase III TIGER-1 trial in the American Thoracic Society's ***American Journal of Respiratory and Critical Care Medicine***.

At the end of 24 weeks, the study found that denufosol patients had better lung exhalation rates than placebo patients, whose exhalation volumes remained relatively unchanged from baseline. A second, longer Phase III trial is ongoing.

MANHATTAN PHARMACEUTICALS' AST-915 – failed in tremor trial but will test higher doses

AST-915 missed the primary endpoint in a randomized, double-blind, placebo-controlled, crossover design, Phase I/II trial in essential tremor. The study, which was conducted at the National Institute of Neurological Disorders and Stroke (NINDS) at the National Institutes of Health (NIH) under an agreement between NIH and Ariston Pharmaceuticals, a wholly owned subsidiary of Manhattan Pharmaceuticals,

measured the effect on tremor power using accelerometry at various time-points after treatment.

AST-915 failed to show a statistically significant effect on tremor power at 80 minutes after administration (the primary endpoint), but there was a statistically significant reduction in tremor at several later time-points up to 300 minutes post-administration. The company called this proof-of-concept and said higher doses will be tested.

NIH reportedly intends to present more details at the 15th International Congress of Parkinson's Disease and Movement Disorders in Toronto, Ontario, in June 2011.

Medicaid – how states can save money

Medicaid is one of the few pharmacy benefit programs that still relies heavily on a fee-for-service approach. Most health plans use third parties to negotiate pharmacy payments with chain drugstores and drug wholesalers, but most state Medicaid programs use a different approach, with public officials helping to set drugstore dispensing fees and drug costs.

A study by the Lewin Group found that the Florida Medicaid program could save $462 million over the next 10 years by managing pharmacy benefits more like state employee plans, Medicare, Medicaid managed care plans, and commercial-sector employer plans.

The study found that Florida could reduce Medicaid drug costs through better management of the 71% of Medicaid pharmacy costs in Florida that now flow through its fee-for-service program, which would generate savings in four other key areas:

1. Increasing generic drug dispensing from the current 67% to the national Medicaid average of 80%.
2. Reducing dispensing fees from the current $3.73 per prescription to the ~$2 paid by Medicare Part D and other health plans.
3. Reducing reimbursement for medications, which typically is higher in Medicaid than Medicare Part D.
4. Reducing the number of prescriptions dispensed per person by imposing more effective controls on polypharmacy, fraud, waste, abuse, etc.

Contrary to conventional wisdom, the Lewin study found that state Medicaid fee-for-service programs *across the country* that pay high dispensing fees often also pay high drug (ingredient) costs and typically do no better at getting generic drugs dispensed. Market-based negotiations could be used, they found, compromising quality or access to medications for patients.

Florida is not unique. Many of these savings could be achieved elsewhere. The question is whether states will do this.

MEDTRONIC's CoreValve

- **Received a CE Mark** for implantation of this trans-catheter aortic valve through subclavian access. The company said it will start training European physicians on this approach in a few weeks.
- **Ethical questions raised in study.** After the PARTNER trial showed Edwards Lifesciences' Sapien was more effective than medical management in elderly inoperable patients, the question is whether it is ethical for Medtronic to continue to randomize CoreValve vs. medical management. The company is discussing with the FDA proposed changes to the U.S. study.

NANOSPHERE's Verisens – highly sensitive test predictive in heart failure

A study released by the ***European Journal of Heart Failure*** found even tiny changes in troponin I – in the nanogram per liter range – have prognostic value in heart failure patients. The Veterans Affairs Effects of Therapy study, which was performed at the Veterans Affairs San Diego Medical Center, followed 144 acute heart failure patients from hospital admission to 90 days post-discharge.

Using this more sensitive assay, troponin levels could be measured in all the patients; before this assay, levels were too low for quantification in some patients. They reported that even at small nanogram levels, increases in troponin I were significantly associated with increased risk of mortality and readmission, and patients with increasing troponin levels during treatment had higher mortality rates than those with stable or decreasing levels. In contrast, BNP was measured, but there was no statistically significant association with mortality.

The researchers concluded:

- Troponin levels are measurable in virtually all heart failure patients with the use of a highly sensitive assay.
- Even small elevations in troponin during hospitalization for heart failure are associated with increased 90-day mortality and readmission.
- Serial increases in troponin concentrations during hospitalization are associated with higher mortality than stable or decreasing levels.

How will the new troponin assay be used? Probably in combination with BNP to help identify a previously unidentified subgroup of high-risk patients who need closer monitoring in hospital and post-discharge.

PFIZER

- **Sutent (sunitinib) – no survival benefit added to Tarceva in NSCLC.** Adding Sutent to Roche's Tarceva (erlotinib) did not improve overall survival vs. Tarceva alone in advanced non-small cell lung cancer patients in a 960-patient Phase III study. The results were reported by Washington University researchers at the Chicago Multidisciplinary Symposium in Thoracic Oncology. Median survival was 9.0 months vs. 8.5 months for Tarceva alone (p=Nss). However, the combination did improve two secondary endpoints:
  - Objective response rate (ORR) was 10.6% with the combination vs. 6.9% for Tarceva alone (p=0.0471).
  - Progression-free survival (PFS) was 3.6 months vs. 2.0 months.
- **Thelin (sitaxsentan) – pulled from market for liver toxicity.** Pfizer is pulling this oral pulmonary arterial hypertension (PAH) drug off the worldwide market, stopping all clinical trials, and withdrawing its FDA application for approval after two patients died of liver failure and a review of clinical trial and postmarketing data showed a new link to liver damage. Pfizer obtained Thelin, which is approved in the European Union, Canada, and Australia, with its 2008 acquisition of Encysive Pharmaceuticals. The FDA never approved Thelin due to safety concerns, and instead three times issued approvable letters asking for more safety data. Liver damage was a known side effect of Thelin and similar endothelin-A receptor antagonists, but the new data suggest the risk is more serious than previously thought.

ROCHE/GENENTECH's Avastin (bevacizumab) – FDA starts breast cancer indication removal process

The FDA is recommending removing the cancer drug Avastin's indication for HER2-negative metastatic breast cancer. It is the first step toward removing the breast cancer indication for the cancer drug Avastin. The company was notified in writing and has 15 days to ask for a hearing in order to dispute the FDA's recommendation.

Dr. Janet Woodcock, director of the FDA's Center for Drug Evaluation and Research (CDER), said that the drug does not lengthen the life of breast cancer patients and can cause severe side effects, including the risk of stroke, wound healing complications, organ damage or failure, and the development of a neurological condition called reversible posterior leukoencephalopathy syndrome (RPLS), which is characterized by high blood pressure, headaches, confusion, seizures, and vision loss from swelling of the brain. Dr. Woodcock said that on the basis of all available data, the drug's risks outweigh its benefits.

Dr. Woodcock said that patients taking Avastin will not be affected immediately, "The FDA is ready to work with Genentech on any proposals to conduct additional trials…[This] announcement is the first step in a process and will not have an immediate impact on the use of Avastin to treat breast cancer or the drug's availability…I want to assure patients and doctors that Avastin's approval for [other cancers] have in no way been affected by [this] announcement."

Dr. Woodcock said that the FDA's decision was difficult but not unique and was based on the science available to the FDA, "What is considered safe may vary depending on the severity of the disease being treated…Cancer drugs ordinarily have serious side effects. FDA understands that some serious risks from cancer drugs are acceptable to patients…FDA's decision …is based on the totality of the data from four clinical studies…Each study was designed to evaluate or measure Avastin's safety and effectiveness in women with HER2-negative metastatic breast cancer…Patients treated with Avastin did not live any longer than patients not treated with the drug…and they were at greater risk for experiencing severe side effects, such as perforation in the stomach and intestines…Other severe side effects…have been observed in patients treated with Avastin."

Dr. Woodcock said that reimbursement was not part of the Agency's decision, and CMS will not be making any reimbursement changes to Avastin and will wait for the process to conclude before making any changes.

Dr. Richard Pazdur, director of the FDA's Office of Oncology Drug Products, said, "I understand that [this] recommendation is…disappointing for breast cancer patients. Please understand that it is disappointing for the FDA as well…We have concluded that the benefits of Avastin in delaying progression of disease have not been shown to translate into prolonged survival of patients…Given the number of serious and life-threatening side effects the FDA does not believe that there is a [good] risk:benefit profile…FDA is open to review data from clinical studies…If successful, such studies could allow the FDA to approve an indication for treatment…in a subpopulation of patients who have been identified."

Dr. Patricia Keegan, director of the FDA's Division of Biologic Oncology Products, discussed the four clinical trials of Avastin in metastatic breast cancer, which enrolled more than 3,000

women. She summarized that there was no survival benefit in patients taking Avastin vs. placebo, "None of the studies showed that Avastin added to standard therapy resulted in additional survival." She said that there was increase in hypertension, hemorrhage, perforation, and other side effects and a 14%-20% increase in NCI common terminology toxicities designated as severe or life-threatening in patients taking Avastin compared to those on placebo."

Denise Esposito, deputy director of the FDA's Office of Regulatory Policy, explained the process, saying that the FDA sent a letter to Genentech. The company has 15 days in which to request a hearing, and if it requests a hearing, it has 30 days to submit a package on which it will rely at the hearing. The hearing is not automatic; the Agency requires that the company establish that there are material facts in dispute that require a hearing. If the FDA grants a hearing, it will announce the date and time, "The format would be a public hearing…but as modified slightly by our accelerated approval regulations. It's not a formal evidentiary hearing. It would be presided over by the Commissioner or her designee, and there would be an advisory panel present." The company would give a presentation, and there would be Q&A. After the hearing, the Commissioner and the FDA participants would evaluate the hearing and render a decision in writing.

Asked about the role of the advisory committee at such a hearing, Esposito said that it would not necessarily be the same advisory committee which previously deliberated on Avastin – the Oncologic Drugs Advisory Committee (ODAC).

Asked if there is an example from the past on how long the process might take, Esposito said, "This is an unusual process. We have not done this in the recent past…Genentech will have 15 days to request a hearing and then up to 30 days to submit the package. The Agency will then deliberate whether to have the hearing…I can't comment on precisely how long [setting up the meeting] would take, but it won't be in the next 30 to 60 days." She added that the docket opened [for this] also is set up to take public comment.

Asked about the European Medicines Agency (EMA) retaining the approval for Avastin for metastatic breast cancer based on the same data, Dr. Pazdur said, "One has to take a look at the issue. Our approval of Avastin in breast cancer was an accelerated approval…The EMA has a similar program called 'conditional approval.' This was not used in this situation, so their initial approval for the drug based on the E2100 trial was a regular or full approval…The contingencies of our accelerated approval were for the demonstration of clinical benefit…to be demonstrated in the AVADO and RIBBON-1 trials. These data have also been submitted to the EMA, and they have ***not*** agreed to any labeling extension, therefore supporting our view that Avastin in this area does not convey clinical benefit."

Asked what was submitted by Genentech in its extension request, Dr. Woodcock said that everything submitted was taken into account by the FDA. She said that the FDA is interested in targeted therapy, "We don't doubt that this drug doesn't have any action in breast cancer, but it does not translate into a survival benefit…There is some tumor response; we agree with that. So, the question is whether there is a subgroup of patients whose tumors are responsive to the drug…or perhaps the tumors respond but the relapse is very fast…and the tumors overcome the intervention. But right now it is not a targeted therapy…We have reviewed all the data – all the scientific information submitted to us we have looked at – and this is our conclusion."

Asked if there is precedent for what will happen to people on the drug, Dr. Pazdur said, "This is a process that has been set in motion. The indication has not been removed, and we would encourage patients to discuss with their physicians what the appropriate course of action should be."

Asked to clarify the EMA issue, Dr. Pazdur said, "Our approval of Avastin was under our accelerated approval program…We had concerns by the fact that we had a large effect on PFS without a demonstrated survival advantage…and there were missing data …We were very concerned about getting additional data…seeing if the 5-month improvement in PFS could be replicated in other studies…We asked for additional data to be submitted, and that identical data were submitted to the EMA. It is my understanding that the EMA is not going to grant additional indications…nor are they going to continue their labeling claim of Avastin plus docetaxel…So, the EMA agrees with us that these additional trials do not convey clinical benefit."

Asked about the role or importance of the survival endpoint and whether it was part of the condition of approval, Dr. Pazdur said, "The conditions of the accelerated approval were to demonstrate a similar magnitude of improvement of progression-free survival or an improvement of overall survival. None of the trials showed an improvement in overall survival, and the AVADO and RIBBON-1 trials failed to disclose the same magnitude of benefit that was demonstrated in the E2100 trial."

If the hearing is held and the outcome is the same, would it still be the first time under an accelerated approval that the whole process will be done? Dr. Woodcock said, "This is not the first time that the Agency has initiated the process of withdrawing an accelerated approval drug or indication. If the hearing were to occur, it

would be the first time that a manufacturer did not agree to withdraw voluntarily and the hearing process [happened]… There have been other notices of opportunity for a hearing on drugs…and those are in the public record."

Asked if any of the four studies pointed to a subgroup of patients who might benefit from Avastin, Dr. Keegan said, "There was no subset that appeared to be different from the general trial results in terms of patients not deriving benefit or deriving a substantially greater benefit."

Dr. Woodcock concluded, "I believe there are still some questions about the differences in approval between the European authorities and where the FDA is…Let me make it clear that as far as the analysis of survival, we had four trials. None showed the drug prolonged life in people with metastatic breast cancer…The EMA's original approval…was a full approval. They accepted that magnitude of progression-free survival as predicting a clinical benefit…FDA said…that magnitude of progression-free survival could be associated with clinical benefit, but it would have to be associated with a magnitude of survival benefit…As far as we could tell, there was no symptomatic benefit to any patient, there were severe side effects, and there was no benefit in terms of survival in any of the trials…The subsequent trials did not show a benefit. Because we did an accelerated approval…Now, we look at the totality of the data in metastatic breast cancer, and we see no overall survival, no evidence of symptomatic benefit to patients, and we see that the benefit compared to the risk of the drug in this particular patient population is not positive… What I hope people take away [is that] none of the four trials shows any survival benefit…but it added many serious side effects, and so that's sort of the bottom line."

Roche immediately responded that Genentech ***will*** request a hearing to maintain Avastin as a treatment option for metastatic breast cancer and emphasized that "until the conclusion of these proceedings, Avastin remains FDA-approved for use in combination with paclitaxel for the first-line treatment of metastatic HER2-negative breast cancer."

SANOFI-AVENTIS

- The first non-French head of research for this pharma, effective January 1, 2011, will be former National Institutes of Health (NIH) director Dr. Elias Zerhouni, a Johns Hopkins School of Medicine radiologist.
- **Anzemet (dolasetron mesylate) – safety warning.** The FDA warned physicians not to use the injectable form of Anzemet to prevent nausea and vomiting in patients undergoing cancer chemotherapy because new data indicated the drug can cause life-threatening cardiac arrhythmias. However, the FDA said the oral form may be used in chemotherapy patients, and a lower dose of the injectable version may be used to prevent postoperative nausea and vomiting. Cancer chemotherapy will now be a contra-indication for the injectable form.

SYNDAX PHARMACEUTICALS' entinostat – failed Phase II trial but hope in a subset of patients

A 132-patient Phase II study reported at the Chicago Multi-disciplinary Symposium in Thoracic Oncology failed to show any prolongation of progression-free survival or overall survival in patients with advanced non-small cell lung cancer (NSCLC) by adding entinostat, a histone deacetylase (HDAC) inhibitor, to Roche's Tarceva (erlotinib). However, the combination did significantly improve response in a subset of patients with high levels of the epithelial marker E-cadherin. In those patients, median overall survival was 9.4 months vs. 5.4 months for Tarceva alone (p=0.03). There was no survival difference in patients with low E-cadherin levels. A follow-up study is expected to start in 2H11.

U.K.'s NICE – rejects several cancer drugs

- **ROCHE's Avastin (bevacizumab) –** The U.K.'s National Institute for Clinical Excellence (NICE) rejected this VEGF inhibitor for colorectal cancer, saying the benefits don't justify the cost and that its decision is final.
- **GLAXOSMITHKLINE's Tyverb (lapatinib, sold as Tykerb in the U.S.) and ROCHE's Herceptin (trastuzumab) –** NICE rejected both of these drugs for metastatic ER+, HER2+ breast cancer patients, saying they don't offer enough value to justify the cost.

REGULATORY NEWS

CMS – P4P works

The Centers for Medicare & Medicaid Services (CMS) reported that the results from three pay-for-performance demonstration projects – one for large physician practices, one for small/solo physician practices, and one for hospitals – found that offering providers financial incentives for improving patient care increased quality of care and reduced the growth in Medicare expenditures.

Among the other findings:

- Hospitals
  - Participating hospitals improved performance across the board.

- An independent evaluation found that quality improved at the participating hospitals, but quality also increased substantially for similar hospitals that were not participating in the demonstration. Only 10%-17% of the quality increase in participating hospitals could be attributed to the pay-for-performance incentives.
- Hospitals that received incentive payments raised their quality score by an average of 18.3% over 5 years vs. 18% for hospitals not receiving incentives.

- Physician group practices
  - All 10 participating physician groups achieved benchmark performance on at least 29 of the 32 measures reported in Year 4. Three groups achieved all 32 benchmarks.
  - All 10 physician groups achieved benchmark performance on the 10 heart failure and seven coronary artery measures. On average, over four years they increased quality scores 10% for the 10 diabetes measures, 13% on the seven heart failure measures, 6% on the seven coronary artery disease measures, 9% on two cancer screening measures, and 3% on three hypertension measures.
- Small/solo practices
  - In the second year of the demonstration, >500 participants are receiving performance rewards on 26 quality measures.
  - The demonstration included an additional bonus for practices that reported the data using an electronic health record (EHR) certified by the Certification Commission for Health Information Technology (CCHIT), and 26% of practices were able to submit at least some of the measures from a certified EHR.

CMS gives EPs their own code – differentiates services

CMS approved a physician specialty code for cardiac electrophysiology (EP), for which the Heart Rhythm Society has been lobbying. Prior to the new code, there was no way for CMS to differentiate EP services from services provided by other cardiologists in the Medicare claims database. CMS designated physician specialty code number 21 for cardiac EP.

FDA easing generic approvals – proposal reduces inspections

According to Russell Wesdyk, scientific coordinator in the FDA's Office of Pharmaceutical Science, the FDA has proposed reducing the number of pre-approval factory inspections for generic drug manufacturers. Instead, the FDA would rely on periodic inspections that focus on the firm's manufacturing in a broader sense. In return, the generic companies would start paying FDA fees.

FDA makes combination products a little easier – guidelines target serious illnesses

The FDA issued new draft guidelines for combination products involving two or more unapproved drugs that may make it easier for them to get approved, but only in serious illnesses such as cancer or AIDS, where combination therapy is needed to overcome resistance or a weak response to only one medicine. Previously, the merits of each component had to be proven first. The draft guidelines specify what types of studies will be needed for approval of these combinations. The FDA will accept public comments until February 14, 2011, and a final version may be released within six months.

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)
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