TRENDS-in-MEDICINE

November 7, 2010

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Quick Takes

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

SHORT TAKES

- **ARTHROCARE's Spartan PEEK Suture Implant** system received FDA 510(k) clearance to reconnect rotator cuff tendons and bone.
- **ATMI** has acquired **Artelis**, a Belgian biotechnology company specializing in bioprocesses and technologies for cell culture research and manufacturing scale-up. The two companies partnered in 2006, so the acquisition is not a surprise.
- **BAYER** reportedly is looking to acquire **Biocompatibles International**.
- **BIODEL's Linjeta (formerly VIAject, a fast-acting human insulin)** was rejected by the FDA, which wants two additional Phase III studies of safety and efficacy of the drug's commercial formulation in both Type 1 and Type 2 diabetics.
- **BIOGEN IDEC** is restructuring and cutting 13% of its workforce worldwide.
- **BOEHRINGER INGELHEIM's Pradaxa (dabigatran)**, an oral thrombin inhibitor that will compete with warfarin, was approved on October 27 by Health Canada. It became available in U.S. pharmacies on November 3. An analysis published in the ***Annals of Internal Medicine***, using data from Medicare and the pivotal RE-LY trial, found that Pradaxa is cost-effective even if retail priced at $13.00 a day for the 150 mg BID dose, which would give it a quality-adjusted life year (QALY) rate of $45,372. And the actual cost is lower since the wholesale cost is ~$6.75 a day.
- **BRISTOL-MYERS SQUIBB's BMS-817378**, a potential cancer treatment, will be developed in conjunction with China-based **Simcere Pharmaceutical Group**, which will have the exclusive rights to develop and sell the drug in China.
- **CADENCE PHARMACEUTICALS' Ofirmev (IV acetaminophen)** was approved by the FDA for relieving pain and fever after surgery.
- **CARDIONET's Mobile Cardiac Outpatient Telemetry system –** The Centers for Medicare and Medicaid Services (CMS) approved national reimbursement of ~$800 for this technology for diagnosing heart arrhythmias, effective in January 2011.
- **CATALYST PHARMACEUTICAL PARTNERS' CPP-115 –** The company reported positive preclinical safety and efficacy results – and a significantly improved retinal safety profile – vs. vigabatrin (the only other commercially available GABA-aminotransferase inhibitor), supporting use in both epilepsy and stimulant addiction. CPP-115 also was found to be orally absorbed, not metabolized. The company plans to initiate the remaining studies necessary for an IND in 3Q11.

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- **DISCOVERY LABORATORIES' Surfaxin (lucinactant)**, an aerosolized KL4 surfactant, was granted orphan drug status by the FDA for the treatment of cystic fibrosis.
- **ELA MEDICAL**, a pacemaker manufacturer, is paying $9.2 million to resolve claims that it paid kickbacks to South Florida doctors and hospitals.
- **GE HEALTHCARE** is acquiring the assets of **Orbotech Medical Solutions**, a subsidiary of Orbotech and a manufacturer of cadmium zinc telluride detectors used in GE's Alcyone nuclear medicine technology.
- **Healthcare reform –** A Republican-led House of Representatives may vote to repeal the healthcare law early next year, but it is extremely unlikely to get through the Senate, so the speculation is that House Republicans will try to deny funding for reform proposals.
- **IMAGING3's Dominion**, a volumetric imaging scanner that can produce 3-D images, was rejected by the FDA which said the device did not match predicated devices cited in the 510(k) application.
- **JOHNSON & JOHNSON** is investigating possible contamination issues at **Crucell**'s South Korean drug facility. Crucell, which is being acquired by J&J, put a temporary hold on all shipments of two vaccines made at that plant.
- **JOHNSON & JOHNSON's Concerta (methylphenidate) –** J&J did a deal under which **Watson Pharmaceuticals** will be the exclusive distributor of an authorized generic of Concerta, a therapy for attention deficit/hyperactivity disorder, from May 2011 through 2014. J&J will manufacture Concerta for Watson and receive a portion of the net sales.
- **MCKESSON** is buying privately-held **US Oncology** to expand its services in the cancer arena. Texas-based US Oncology is affiliated with >1,300 oncologists.
- **MEDTRONIC's Octopus Nuvo Tissue Stabilizer –** The FDA classified the recall as a Class I because of a "reasonable probability" of the device causing serious injury or death. Medtronic pulled the device from the market in September 2010 and is retrieving the 571 devices in the U.S., Europe, and Canada.
- **MERCK's Zostavax shingle vaccine –** Production issues caused a shortage of the vaccine, resulting in some patients (*including a* ***Trends-in-Medicine*** *staff member*) having to wait as long as 10 months for the vaccine. Orders placed from mid-May through September 2010 are expected to be shipped later this month or in December 2010.
- **NOVARTIS's Afinitor (everolimus)**, which is approved to treat kidney cancer, was approved by the FDA for the treatment of subependymal giant cell astrocytoma (SEGA), a benign brain tumor associated with a rare genetic condition, in patients who are not candidates for surgical resection.
- **OCTAPHARMA** is conducting a prospective, randomized, active-controlled, open-label, multicenter Phase II trial in the U.S. and Germany of this recombinant Factor VIII derived from a human cell line (human-cl rhFVIII) in patients with severe hemophilia A, the most common form of hemophilia. The study is assessing pharmacokinetics, efficacy, safety, and immunogenicity.
- **Pediatric oncology drugs –** The Pediatric Oncology Subcommittee of the FDA's Oncologic Drugs Advisory Committee will discuss pediatric development of four products that were either recently approved by FDA or are in late stage development for an adult oncology indication: Pfizer's crizotinib, Allos Therapeutics' Folotyn (pralatrexate), Amgen's denosumab, and Eisai's eribulin.
- **STRYKER** is acquiring privately-held **Porex Surgical**, a division of Porex Corp., which makes products for the craniomaxillofacial surgery market.
- **UROPLASTY's Urgent PC Neuromodulation System –** CMS has decided to pay for this overactive bladder treatment, a posterior tibial nerve stimulation.
- **WATERS** is launching a new "Centers of Innovation Program" to support more collaborative research with scientific experts worldwide using UltraPerformance Liquid Chromatography (UPLC) in the areas of health and life sciences, sports science, food safety, clinical research, and environmental protection.

NEWS IN BRIEF

Alzheimer's disease – a step forward in diagnosis

The presence of small, soluble oligomers of amyloid-β (Aβ), the most toxic form of the peptide, in the cerebrospinal fluid (CSF) could be an early sign of impending Alzheimer's disease. However, measuring these peptides in biological samples has been very difficult, but an article in the journal ***Neurology*** indicated that scientists have made some headway in measuring similar peptides in Parkinson's disease (PD) patients using an antibody-based test (ELISA) developed by researchers in the United Arab Emirates. The same approach may be able to be used to test for Aβ.

In addition, researchers in Japan and at the University of Tennessee Medical Center are making progress on a valid test for Aβ oligomers using antibodies. A Swedish company, **BioArctic Neuroscience**, is developing an Aβ protofibril-specific antibody as both a diagnostic tool (AβN) and a

therapeutic (BAN2401) for Alzheimer's, and an 80-patient therapeutic trial has just begun.

ANTISENSE PHARMA's trabedersen (AP-12009) – a promising therapy for malignant glioma

Despite surgery, radiotherapy, and chemotherapy most malignant brain tumors recur, and the patients die within a few months, but a Phase IIb study of trabedersen suggested that this antisense agent which selectively downregulates TGF-β2 may extend survival. There was no improvement in overall survival, but in a pre-specified subgroup of patients (≥age 55 and Karnofsky Performance Status >80%) with anaplastic astrocytoma, the efficacy was pronounced vs. standard chemotherapy. Tumor control also was significantly better with trabedersen.

The study was published in the journal ***Neuro-Oncology***. A pivotal, international, 132-patient, Phase III SAPPHIRE trial is ongoing in recurrent/refractory anaplastic astrocytoma patients and soon will begin enrolling U.S. patients with high-grade glioma.

Phase IIb Results with Trabedersen in Anaplastic Astrocytoma

Measurement	Trabedersen 10 µM	Chemotherapy	p-value
Tumor control at 14 months	58%	0	0.0032
Overall response	N/A	N/A	0.0337
Duration of response	29.1 months	8.0 months	Nss, p=0.10
2-year survival	83.3%	41.7%	---
Overall survival	39.1 months	21.7 months	Nss

BAYER/JOHNSON & JOHNSON's Xarelto (rivaroxaban) – positive top-line results

Xarelto, a Factor Xa inhibitor, met the primary endpoint in the pivotal ROCKET-AF study in atrial fibrillation, showing non-inferiority to warfarin on stroke and systemic embolism and a comparable rate of major and non-major clinically-relevant bleeding. The full details will be presented at the American Heart Association meeting on November 15, 2010. The things to watch in those data are:

- Was there superiority or just non-inferiority to warfarin on the primary endpoint.
- What were the rates of major and intracranial bleeding.
- Adverse events, particularly ALT and bilirubin increases.

BRISTOL-MYERS SQUIBB's Yervoy (ipilimumab) – delayed

The FDA delayed making a decision on this potential melanoma therapy, moving the PDUFA date to March 26, 2011, from December 25, 2010. The company said the FDA wanted "additional time to review new data about the drug's use in pre-treated melanoma patients…Study results published earlier this year showed average patient survival time was 10 months with ipilimumab vs. just over six months for patients using traditional therapies."

CYBERONICS' VNS Therapy System – the poster child for poor FDA device oversight?

A ***British Medical Journal*** article cited >900 deaths since 1997 with VNS, a vagus nerve stimulator for treatment-resistant epilepsy, as a prime example of the FDA's inadequate oversight of medical devices. The device is still on the market. The company collected mortality data in postmarketing studies but has not reported the results, just responding to the FDA's request that it "characterize morbidity and mortality."

The authors of the article cited this as an "example of the gap in post-approval surveillance of medical devices." In an accompanying editorial, Dr. Jerry Avorn of Harvard Medical School also criticized FDA oversight of devices, "The standards for device approval and surveillance have fallen far below those for drugs, and even those that would be dictated by common sense…It would be unthinkable for a drug company to go to the [FDA] or the European Medicines Agency and say, in effect, 'This new drug is much like an older product we sell, except that we have added a new amine group and modified one of the side chains. Apart from that, it's pretty close, so we won't be doing any new clinical tests on it. When can we begin marketing?' But this is essentially what happens with many new medical devices when they are approved."

Are the deaths due to VNS or to sudden unexpected death from epilepsy (SUDEP), which occurs in 0.7%-0.9% of patients with treatment-resistant epilepsy? About 57,000 VNS devices reportedly have been implanted worldwide, and in that many patients as many as 513 deaths might be expected from SUDEP. But that is half the number reported through the FDA's MAUDE system (for adverse event device reporting) alone.

The FDA has a chance to fix problems like this as it reforms the 510(k) process.

DARA BIOSCIENCES' DB-959Na – positive early results

This oral dual PPAR (delta/gamma) was safe in a randomized, double-blind, placebo-controlled Phase I trial in Type 2 diabetics, with no moderate, severe, or serious adverse events and likely QD dosing. Preclinical studies indicated DB-959Na raises HDL and lowers triglycerides without weight gain. The company plans to initiate a multiple ascending-dose trial in 1H11.

Digital mammography devices – FDA lowers the approval bar

The FDA is easing the pathway for approval of mammography systems that produce computerized X-ray images of the entire breast (Full Field Digital Mammography Systems). When these devices were first approved in 2000, they were categorized as high-risk Class III devices, requiring a PMA for approval. The FDA said that digital mammography is now well-validated, so the devices are being reclassified as Class II (medium-risk) devices, which means they may be able to be approved under the FDA's less rigorous 510(k) program.

The FDA also released "special controls" guidance for industry describing what evidence will be needed to show substantial equivalence for these systems under a 510(k) application.

So far, the FDA has approved five full field digital (FFD) mammography systems – all as Class III devices – and the FDA estimates that ~70% of mammography units in use today are digital, with 70% of certified U.S. mammography facilities having ≥1 digital unit.

Drug prices – lowering them improves compliance/adherence

Two studies published in ***Health Affairs*** magazine found that lowering prices for prescription drugs used for a chronic illness improves adherence but may not ultimately reduce drug spending or lead to better outcomes. The authors cited the example of Pitney Bowes, which ended copays for statins for employees who had diabetes or vascular disease, and the employees' adherence to the drug regimen increased by 2.8%. But they also cited a study by Blue Cross Blue Shield of North Carolina which found similar results when copays were terminated for generic drugs and reduced for brand name drugs for treating certain diseases, including diabetes and congestive heart failure.

Drug-coated balloons – gaining popularity

Drug-coated balloon technology is starting to find use by interventional cardiologists in Europe for niche applications, and Millennium Research Group predicts the market will continue to grow as physicians find more niches. Although there are not as much data on drug-coated balloons as for drug-eluting stents (DES), doctors are using drug-coated balloons where DES cannot be used, such as in patients who can't take dual antiplatelet drugs or for bifurcations or in-stent restenosis. The results of several ongoing clinical trials also have the potential to affect use of drug-coated balloons:

- Eurocor's VALENTINES trial of its paclitaxel-coated Dior balloon.
- Lutonix's PERVIDEO-I trial of its paclitaxel-coated Lutonix balloon.
- B. Braun's PEPCAD trial of its paclitaxel-coated Coroflex balloon.

ENDO PHARMACEUTICALS' Opana TRF (oxymorphone extended-release) – FDA panel has implications for other pain drugs

The FDA's Anesthetic and Life Support Drugs Advisory Committee and the FDA's Drug Safety and Risk Management Advisory Committee will meet jointly on December 2, 2010, to consider whether Opana TRF should be approved for the relief of moderate-to-severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time. The PDUFA date is January 7, 2011.

This is the same formulation (developed by Grünenthal) that J&J hopes to use for its Nucynta ER (tapentadol ER), but J&J got a complete response letter from the FDA asking for additional information. If Nucynta ER isn't approved before the panel, the advisory committee could provide some useful insights into FDA's level of comfort with this formulation and potential issues, such as susceptibility to chewing.

Gastrointestinal stromal tumors (GIST) – therapy of this rare disease has improved

Fewer than 6,000 people in the U.S. are diagnosed annually with GIST, which represents only ~1% of all GI cancers, making it a rare disease. Interest in GIST has increased recently, due in part to greater awareness and detection.

The standard treatment for metastatic GIST today is first Novartis's Gleevec (imatinib) and then Pfizer's Sutent (sunitinib). Prior to these tyrosine kinase inhibitors (TKIs), the response rate to chemotherapy was 5%, but now the majority of patients with stable disease will do well, often for a long

time. During a Pfizer-sponsored teleconference, Dr. Suzanne George, a sarcoma specialist from Dana-Farber Cancer Institute, said, "Most patients tolerate [Gleevec] quite well… [But] there is a small percentage of patients who are resistant to imatinib upfront, and it is important to identify those patients because there are other therapies."

Dr. Jonathan Trent, a sarcoma specialist from MD Anderson Cancer Center, said the effect of the TKIs is analogous to turning off a light switch, "It is not that simple, but that is a useful analogy."

Mutational testing may become more important in GIST in the future, particularly for exon 11 and exon 9 mutations. Asked if mutational testing is realistic for a community oncologist, Dr. George said, "It is increasingly available across the U.S…It is a great way to gain additional information…I do think it is important and realistic. Both European and U.S. guidelines encourage mutational testing for GIST…Most – but not all – insurance companies will reimburse for it…Where mutation testing is less clear is in the setting of resistance."

Managing adverse events in GIST also has moved forward. The key side effects with Gleevec are diarrhea, muscle cramping, nausea, and some rash. Sutent has a different adverse event profile: hypertension, hypothyroidism, fatigue, diarrhea, oral hypersensitivity, and hand-foot skin reactions. Dr. George said the oral hypersensitivity is not mucositis or stomatitis but sometimes requires diet modifications, such as eliminating carbonized beverages and extremely hot or cold foods.

HEALTHCARE IT – security still not a priority

Hospitals and medical practices are spending to secure patient information, according to the 2010 HIMSS Security Survey, but they are spending less than other industries on security. About half the respondents said their organization spends ≤3% of the IT budget on information security, which is comparable to 2009 survey results. However, respondents also indicated that their security budgets increased in the last year, due at least in part to federal incentives.

Other survey findings included:

- ≥50% of hospital respondents reported using ≥2 types of controls to manage data access vs. 40% of medical practice respondents.
- Mobile device encryption, email encryption, and single sign-on were the technologies least frequently installed but planned for future installation. Hospitals are more likely to install them in the future than medical practices.
- ~85% said their organization shares patient data electonically.
- 33% reported that their organization had at least one known case of medical identity theft.
- On a scale of 1 (low) to 7 (high), the average security environment rating was 4.43.
- Half of respondents validate patient identity by requiring both a government/facility-issued ID and checking the ID against information in the master patient index.

HOSPIRA's Symbiq – infusion pump recall stepped up

The FDA issued a Class 1 recall of these infusion pumps because of failures of the motor encoder in the pumping mechanism that can cause the infuser to stop working, resulting in serious injury or death. In February 2010, Hospira notified customers of an Urgent Device Field Correction, and this was updated in October 2010, but this situation has now been upgraded to a more serious warning. Until Hospira can upgrade all Symbiq pumping mechanisms, the FDA said corrected loaner pumps will be provided at no cost to customers for critical care areas. Until those loaners or corrected pumps are in place in critical care areas, Hospira is urging customers to consider using an alternate way to administer therapy.

JOHNSON & JOHNSON/ETHICON – challenging an FDA rejection

J&J asked FDA Commissioner Dr. Margaret Hamburg to allow it to appeal the Center for Devices and Radiological Health's rejection of J&J's Sedasys computer-aided sedation device, which is used in colonoscopy and upper gastrointestinal procedures, despite the Anesthesiology and Respiratory Therapy Devices Advisory Committee voting 8-2 in favor of approval. If Dr. Hamburg grants the appeal, the FDA would appoint a new, independent advisory committee and hold a public hearing on Sedasys. *It's a risky move; CDRH has a long memory.*

KADMON PHARMACEUTICALS – Sam Waksal returns

Kadmon was formed by former ImClone Systems chief executive Samuel Waksal, PhD. The company, which plans to do its own R&D as well as acquire products, will focus on cancer, infections, and autoimmune diseases. Kadmon already acquired Three Rivers Pharmaceuticals, which specializes in hepatitis drugs, and it is expected to announced the in-licensing of an experimental hepatitis C drug from Valeant Pharmaceuticals.

MANNKIND's Afresa (inhaled insulin, formerly Technosphere) – accused of monkey business

A former senior manager, John Arditi, filed suit against Mannkind, saying he was wrongfully fired after uncovering serious problems – "potential fraud and scientific misconduct" – with clinical trials of Afresa. His suit claimed that a Russian site enrolled patients in the study who "had the same blood pressure readings at each visit for several months," which is "unlikely to be an accurate finding and raised the chance of fraudulent study results, including the possibility of fictitious patients." The company said the allegations are "without merit," and the company intends to "defend against them vigorously."

Metformin – may prevent or control lung cancer

In a study presented at the American College of Chest Physicians, researchers reported that metformin may help control and even prevent lung cancer. And patients who do develop lung cancer on metformin may get less advanced cancer. In a chart review of 157 lung cancer survivors with diabetes, those on either metformin or a TZD – i.e., Takeda's Actos (pioglitazone) or GlaxoSmithKline's Avandia (rosiglitazone) – were significantly less likely to develop metastatic lung cancer than patients not taking the diabetes drugs (20% vs. 42%). In addition, squamous cell and small cell carcinomas occurred less often in metformin patients.

PFIZER

- **Dilantin (phenytoin IV)** and **Cerebyx (fosphenytoin) – FDA panel considers side effects.** The FDA's Peripheral and Central Nervous System Drugs Advisory Committee recommended that Dilantin be labeled with warnings that it can cause Purple Glove Syndrome (PGS), a condition in which a hand swells, turns purple, and becomes painful. However, the panel voted not to recommend pulling the drug from the market. There is also some risk of PGS with Cerebyx, but the panel was divided on whether there is adequate information to conclude that it also causes PGS.
- **Fablyn (lasofoxifene) – new efficacy data.** This selective estrogen receptor modulator (SERM) was rejected by the FDA last year as an osteoporosis treatment over concerns about a possible increase in all-cause mortality. A new case-control study published in the ***Journal of the National Cancer Institute*** found Fablyn reduced the risk of breast cancer and fractures in postmenopausal women with osteoporosis. Women taking Fablyn had a 79% decreased risk of breast cancer vs. placebo, a 24% reduction in non-spine fractures at the high dose, and a 42% reduction in spinal fractures at the high dose. Researchers at the Fred Hutchinson Cancer Research Center, analyzing 49 cases of breast cancer and 156 unaffected controls from the PEARL trial, also found a 32% reduction in coronary events and a 36% reduction in strokes with Fablyn.

ROCHE's RG-7204 – promising Phase II results in advanced melanoma

The results of the open-label, Phase II BRIM2 study found that this BRAF inhibitor shrank tumors in more than half of patients with BRAF V600E mutation-positive metastatic melanoma. Median progression-free survival (PFS) was 6.2 months vs. 2 months historically. The findings from this single-arm, multicenter, 132-patient study, in which RG-7204 was given BID daily until disease progression, were presented at the International Melanoma Research Congress in Sydney, Australia.

BRIM2 Results with RG-7204 in Metastatic Melanoma

Measurement	RG-7204
Tumor size decrease ≥30% for at least 2 consecutive scans	52%
Primary endpoint: Overall response	52%
CR + PR	22%
SD	30%
Secondary endpoint #1: Median PFS	6.2 months
Secondary endpoint #2: Median duration of response	6.8 months
Secondary endpoint #3: Median overall survival	Not yet reached
Grade ≥3 adverse events	
ALT abnormal	14%
Joint pain/arthritis	11%
GI (dysphagia/pancreatitis)	10%
Most common adverse events	Rash, photosensitivity, hair loss, joint pain
Grade 3 cutaneous squamous cell carcinoma	26% *

*** The lesions were excised, and the patients continued with treatment.**

Roche plans to begin an expanded access program to make RG-7204 available to people with BRAF-mutation positive advanced melanoma who have had at least one prior medicine. Roche is developing a companion diagnostic test – the cobas 4800 BRAF V600 Mutation Test – for the BRAF mutation along with RG-7204.

SEATTLE GENETICS' brentuximab vedotin (SGN-35) – very positive early data

In a 45-patient Phase I trial, brentuximab vedotin regressed tumors in 86% of patients with CD30-positive refractory lymphoma (mostly non-Hodgkin's lymphoma). The open-label, dose-escalation study, which was published in the ***New***

England Journal of Medicine, found that three courses of the monoclonal antibody/drug conjugate increased median progression-free survival (PFS) by 3.8 months (from 5.9 months to 9.7 months). Complete remission occurred in 11 patients, partial remission in 6 more (50% of the patients at the maximum tolerated dose), and the response lasted 17.3 months on average. Symptoms also resolved in 13 of the 16 symptomatic patients.

In terms of safety, one patient given 3.6 mg/kg IV Q3W (the top dose) developed febrile neutropenia and died. The researchers determined that 1.8 mg/kg is the maximum tolerable dose. The most common adverse events were fatigue (36%), fever (33%), and nausea, diarrhea, peripheral neuropathy, and neutropenia (22% each).

Spiral CT – better than chest X-rays for lung cancer screening

Screening smokers with low-dose helical computed tomography (spiral CT) instead of standard chest X-rays resulted in 20.3% fewer lung cancer deaths by detecting the cancer earlier in a large study. The study was stopped early by the independent Data and Safety Monitoring Board (DSMB) because the results were statistically convincing in favor of spiral CT.

The study also found that all-cause mortality was 7% lower in patients screened with spiral CT. About 25% of deaths in the study were due to lung cancer, while other deaths were due to factors such as cardiovascular disease. Researchers couldn't explain this, but they plan to analyze it further.

The National Lung Screening Trial (NLST), a randomized national study of >53,000 current and former heavy smokers aged 55 to 74, was sponsored by the National Cancer Institute (NCI) and conducted by the American College of Radiology Imaging Network (ACRIN) and the Lung Screening Study group. Patients received three annual screenings with either spiral CT or standard chest X-ray.

Dr. Harold Varmus, director of the NCI, said, "A validated [screening] approach that can reduce lung cancer mortality by even 20% has the potential to spare very significant numbers of people from the ravages of this disease. But these findings should in no way distract us from continued efforts to curtail the use of tobacco, which will remain the major causative factor for lung cancer and several other diseases."

Dr. Christine Berg, NLST project officer for the Lung Screening Study, said, "This is the first time that we have seen clear evidence of a significant reduction in lung cancer mortality with a screening test in a randomized controlled trial. The fact that low-dose helical CT provides a decided benefit is a result that will have implications for the screening and management of lung cancer for many years to come."

A more complete analysis will be published in a peer-reviewed journal within the next few months.

Stem cells – progress in MS

In an article published in the ***Archives of Neurology***, Israeli researchers reported that an open-label, 34-patient Phase I/II trial found that mesenchymal stem cell (MSC) grafts were safe, causing no problems when injected into people with amyotrophic lateral sclerosis (ALS) or multiple sclerosis (MS). The researchers collected cells from each participant's bone marrow and cultured MSCs in the lab. Then, they returned the expanded, purified MSCs to the patients via intrathecal injections or intravenously and followed the patients for ≥6 months.

To do any good, MSCs have to find the places where they are needed. In nine of the participants, the researchers tagged the expanded MSCs with iron oxide nanoparticles and used MRI to examine where the cells ended up. They observed labeled cells in the nerve roots, meninges, and parenchyma of the spinal cord, indicating the transplants migrated away from the injection site. In 12 participants, who received both intrathecal and intravenous MSCs, the scientists collected peripheral blood to examine immune activity. They found that following the MSC treatment, 72% more regulatory CD4+ CD25+ T cells were in the veins. However, the population of activated CD40 cells, which can promote inflammation, dropped by half.

Although the primary study endpoint was safety, the authors also looked for any improvement or plateau in disease progress.

- For people with **MS**, they used the Expanded Disability Status Scale, which quantifies how much of the body is disabled. On average, the scores in the MS group improved from 6.7 to 5.9 within six months.
- In **ALS** cases, the researchers used the ALS-Functional Rating Scale, a measure of how well people can complete daily tasks such as speaking and walking, and there was no significant change in the ALS-FRS.

U.K.'s National Institute for Health and Clinical Excellence (NICE) – losing its authority

NICE's ability to deny drugs to National Health Service (NHS) patients because they are not cost-effective will be taken away in 2014. The U.K.'s Department of Health has decided that

general practitioners (GPs) and not NICE should decide what the NHS can afford.

Starting in 2014, the British government will use value-based pricing to negotiate drug prices with pharmaceutical companies. It is hoped this approach will bring down the price of new drugs, so they can be made available in the U.K. while more data are collected on effectiveness. There will no longer be a ban on use of drugs that exceed £30,000 per QALY.

As of 2014, NICE's role will be to advise doctors on which drugs are most effective. Groups of GPs – consortia – will be responsible for deciding whether a drug should be funded or not. These consortia, which will be in charge of spending NHS money in their regions, will be allocated >£70 billion, to be divided up based on population and level of ill-health. Out of this, the consortia will fund ***everything***, from hospital operations and drugs to nursing visits.

The bottom line: There will still be rationing, just regionally instead of nationally.

REGULATORY NEWS

FDA and University of Rochester partnership

The FDA is partnering with the University of Rochester to form the Analgesic Clinical Trial Innovations, Opportunities, and Networks (ACTION) Initiative. This is part of the FDA's effort to streamline the discovery and development process for new analgesic drug products.

This multi-year, multi-phased initiative will address major gaps in scientific information that can slow down analgesic clinical trials and analgesic drug development. Key objectives include:

- Establishing a scientific and administrative infrastructure to support a series of projects;
- Establishing relationships with key expert stakeholders, industry, professional organizations, academia, and government agencies;
- Coordinating scientific workshops with key experts in the field of anesthesia and analgesia;
- Conducting in-depth and wide-ranging data analyses of analgesic clinical trial data to determine the effects of specific research designs and analysis methods.

FDA public meeting on withdrawal of midodrine

In August 2010 the FDA announced it was going to withdraw approval of midodrine hydrochloride, a hypotension drug, because neither the original manufacturer (Shire) nor any generic manufacturer had provided data on the drug's efficacy. The Heart Rhythm Society (HRS) sent a letter to the Agency, complaining about the decision, and the FDA is listening.

HRS noted that the FDA did not identify any safety or efficacy problems with the drug and warning that taking it off the market would "negatively affect the care of ~100,000 patients who are currently receiving this drug." HRS also explained that electrophysiologists prescribe midodrine because it has "substantial effectiveness in the treatment of some patients" and that the few alternative drugs available "have higher side effect profiles."

In response, the FDA announced that it will hold a public hearing to allow Shire to present evidence about ProAmatine's clinical benefit. No date has been announced yet.

In addition, the FDA plans to open a docket where the public can comment on the conduct of clinical trials needed to verify and describe the clinical benefit of midodrine to treat symptomatic orthostatic hypotension. The FDA also said the drug will remain available to patients as it works to obtain the data.

ProAmatine was approved in 1996 under accelerated approval, which allows companies to use a surrogate endpoint for approval but also requires the manufacturer to prove clinical benefit in a post-approval study. Shire did do post-approval studies, but the FDA said the data that was submitted did not verify the clinical benefit.

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
	November 2010	
November 10	Innovations in technology for the treatment of diabetes, focusing on the **artificial pancreas**	FDA public workshop
November 16	**GSK/Human Genome Sciences' Benlysta** (belimumab) for lupus	FDA's Arthritis Advisory Committee
November 17	National Coverage Decision meeting on **Dendreon's Provenge** (sipuleucel-T)	CMS's Medicare Evidence Development and Coverage Advisory Committee (MEDCAC)
November 18	**Amgen's denosumab** for cancer patients	PDUFA date
November 18	**Mela Sciences' MelaFind** for melanoma detection	FDA's General and Plastic Surgery Devices Advisory Committee
November 30	**GlaxoSmithKline/Valeant's ezogabine** for epilepsy	PDUFA date
November 30	Discussion of **pediatric development of four oncology products** that were either recently approved by FDA or, are in late stage development for an adult oncology indication: Pfizer's crizotinib, Allos Therapeutics' Folotyn (pralatrexate), Amgen's denosumab, and Eisai's eribulin	Pediatric Oncology Subcommittee of the FDA's Oncologic Drugs Advisory Committee
	December 2010	
December 1	**GlaxoSmithKline's Avodart** (dutasteride) and **Merck's Proscar** (finasteride) for prostate cancer	FDA's Oncologic Drugs Advisory Committee (ODAC)
December 2	**Bristol-Myers Squibb's Yervoy** (ipilimumab) for advanced melanoma *and* **AstraZeneca/iPR Pharmaceuticals' Zictifa** (vandetanib) for thyroid cancer	FDA's Oncologic Drugs Advisory Committee (ODAC)
December 2	**Endo Pharmaceutical's Opana TRF** (oxymorphone ER) for pain	FDA's Anesthetic and Life Support Drugs Advisory Committee jointly with the Drug Safety and Risk Management Advisory Committee
December 2	**Oceana Therapeutics' Solesta** (dextranomer in gel of stabilized non-animal hyaluronate) for fecal incontinence	FDA's Gastroenterology and Urology Devices Advisory Committee
December 3	**Allergan's Lap-Band,** expanded indication	FDA's Gastroenterology and Urology Devices Advisory Committee
December 7	**Orexigen Therapeutics' Contrave** (naltrexone + bupropion), a diet drug	FDA's Endocrinologic and Metabolic Drugs Advisory Committee
December 9	**GSK/Human Genome Sciences' Benlysta** (belimumab) for lupus	PDUFA date
December 16	**AstraZeneca's Brilinta** (ticagrelor), an anticoagulant	PDUFA date
December 29	**Mannkind's Afresa** (inhaled insulin)	PDUFA date
	Other future meetings	
January 7, 2011	**Endo Pharmaceuticals' Opana TRF** (oxymorphone ER) for pain	PDUFA date
January 31, 2011	**Orexigen Therapeutics' Contrave** (naltrexone + bupropion), a diet drug	PDUFA date
March 7, 2011	**Salix Pharmaceuticals' Xifaxan** (rifaximin) for non-constipation IBS	PDUFA date
March 26, 2011	**Bristol-Myers Squibb's Yervoy** (ipilimumab) for advanced melanoma	New PDUFA date
Date TBA, 2011	Review of **accelerated drug approval process**	FDA's Oncologic Drugs Advisory Committee (ODAC)
Summer 2011	Report on **FDA 510(k) reform**	Institute of Medicine