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

- **AMGEN** reportedly is considering a takeover offer for **Actelion**, which makes pulmonary arterial hypertension (PAH) drugs, in order to gain new medicines for rare diseases.
- **AVEO PHARMACEUTICALS' tivozanib** met key safety goals in a Phase Ib study of 22 patients in combination with FOLFOX6. More than 35% of the 17 evaluable patients had a partial response to this potential gastrointestinal cancer drug.
- **BAXTER's heparin –** An Illinois state court ruled for the plaintiffs in a suit against Baxter over contaminated heparin with ingredients from China. The court called the company's heparin "unreasonably dangerous."
- **BAYER** plans to cut 4,500 jobs by the end of 2012, including 1,700 layoffs in Germany. However, the company also plans to hire ~2,500 people in emerging markets.
- **BIONOR PHARMA's Vacc-4x –** The company plans to resume development of this experimental HIV vaccine after it unexpectedly reduced virus levels. Last month, Bionor canceled the Vacc-4x program when an early study showed patients taking it were just as likely as those receiving a placebo to have to resume antiretroviral therapy. However, further analysis of the study data showed the vaccine triggered an "unexpected" and statistically significant drop in levels of the virus.
- **CARDINAL HEALTH**, a drug wholesaler, plans to buy privately-held pharmaceutical distributor **Kinray** to boost its presence in the northeastern United States. Kinray primarily serves the New York metropolitan area.
- **DENDREON's Provenge (sipuleucel-T) –** The Center for Medicare and Medicaid (CMS) Medicare Evidence Development and Coverage Advisory Committee (MEDCAC) agreed that this therapeutic vaccine is safe and helps prostate cancer patients live longer. If CMS takes the panel's advice, it could cover Provenge for FDA-approved uses. The panel's decision is important because while the drug lengthens survival an average 4.1 months, it costs about $93,000 a year. CMS should make a decision by April 2011.
- **EISAI's Halaven (eribulin mesylate)**, a microtubule inhibitor derived from a sea sponge, was approved by the FDA to treat patients with metastatic breast cancer who have received at least two prior chemotherapy regimens (an anthracycline and a taxane) for late-stage disease. Dr. Richard Pazdur, director of the FDA's Office of Oncology Drug Products, CDER, said Halaven "shows a clear survival benefit and is an important new option for women."

Genetic testing – A recent survey reported at the American Society of Human Genetics meeting found that customers who use direct-to-consumer (DTC) genetic testing kits are

generally satisfied with their experience and with any resultant changes in their attitudes or behaviors. The survey also found a low percentage of respondents misinterpreted risk results.

- **GENZYME** is selling its diagnostic products business to **Sekisui Chemical Co.** of Japan. Genzyme plans to "focus on key areas of future growth," like its product pipeline and rare disease business. Sekisui reportedly will offer jobs to the unit's ~575 employees, including senior management, and the deal is expected to close by the end of the year.

- **HORIZON THERAPEUTICS' HZT-501 (ibuprofen + famotidine) –** In two studies in patients taking long-term NSAIDs, HZT-501 reduced upper gastrointestinal ulcers better than ibuprofen alone, for both the entire study population (14.0% vs. 34.5%, p=0.004) and in a subgroup receiving low-dose aspirin (14.1% vs. 26.5%, p<0.0001). Adverse events were comparable, leading investigators to suggest that HZT-501 might improve compliance, and therefore decrease adverse events, such as gastrointestinal bleeding and hospitalizations.

- **HUMAN GENOME SCIENCES** and **GLAXOSMITHKLINE's Benlysta (belimumab) –** The FDA's Arthritis Advisory Committee voted that Benlysta is safe and effective in systemic lupus erythematosus and should be approved. The panel voted 13-2 in favor of approving it, despite trial design flaws and trial results showing that the drug does not work in African Americans.

- **KV Pharmaceutical** plans to focus on developing branded specialty drugs that require special handling and to consider strategic options for its generic drug business. After "several" recalls, KV pulled all of its remaining products from the market in January 2009. It returned its first product to the market in September 2010 and is trying to gain approval for more products. In other news, former CEO Marc Hermelin, who is banned for 20 years from doing business with the federal government, resigned from the KV board of directors.

- **LEMAITRE VASCULAR** acquired the Lifespan vascular graft manufacturing business from **Angiotech Pharmaceuticals**. Lifespan, a vascular prosthesis used in the repair or replacement of diseased arteries and in the creation of vascular access sites for dialysis, has been sold in the U.S. and other countries through distributors, primarily **Edwards Lifesciences**. Edwards' distribution of Lifespan will end November 30, 2010, and LeMaitre Vascular plans to begin selling Lifespan through its own worldwide sales force on December 1, 2010.

- **Medicaid/Medicare drug prices –** Montana Gov. Brian Schweitzer asked the federal government for permission to sell cheaper prescription drugs in that state through the federal Medicaid program. He said, "The federal government can get cheap drug prices for Medicaid… because of Congress' negotiations with special interest groups…Those prices are far less than the price for those on Medicare, which usually serves the elderly, or private insurance plans…[My] plan would cost the government nothing – and could even save it money – because it would open up the doors for government-subsidized Medicare patients to buy-in at the cheaper Medicaid rate." Health and Human Services Secretary Kathleen Sebelius reportedly told Schweitzer she was "intrigued" by the idea.

- **MELA SCIENCES' MelaFind –** This hand-held melanoma detection device got a "neutral" vote (8 to 7) on approvability from an FDA advisory committee. The FDA reviewers told the panel that the device "may do more harm than good."

- **MERCK's Gardasil** vaccine for human papillomavirus (HPV) was determined to be safe and effective in preventing anal cancer in both males and females ages 9 to 26 by the FDA's Vaccines and Related Biological Products Advisory Committee.

- **MRI –** A study in the ***Journal of Clinical Oncology*** found that magnetic resonance imaging (MRI) is more effective than mammography in early detection of tumors in women with the BRCA mutation or who are at high risk for breast cancer.

- **ROCHE** plans to cut its workforce by 4,800 positions worldwide (6%) over the next two years, to transfer ~800 jobs to other Roche sites, and to outsource 700 positions. The largest reductions are planned in sales and marketing and in manufacturing.

- **TAKEDA** and **JOHNSON & JOHNSON's Velcade (bortezomib) –** The companies voluntarily recalled several batches of this injectable multiple myeloma drug after white polyester-like particles reportedly were found in it. About 200,000 vials were pulled from the U.S. market by Takeda/Millennium, and ~195,000 3.5-milligram vials and 22,300 3-milligram vials were recalled by Johnson & Johnson/Janssen-Cilag in Europe, Japan, and Malaysia.

NEWS IN BRIEF

AMGEN's Xgeva (denosumab) – approved to prevent bone mets

The FDA approved Xgeva to help prevent skeletal-related events (SREs) – fractures and bone pain – in patients with cancer that metastasized to the bone. It is not approved for patients with multiple myeloma or other hematologic cancers.

In making the announcement, the FDA noted that Xgeva was "superior to Zometa" (Novartis, zoledronic acid injection) in patients with breast or prostate cancer. In patients with other solid tumors, time to development of an SRE was similar for both Xgeva and Zometa, the FDA said. Side effects with Xgeva highlighted by the FDA were hypocalcemia and osteonecrosis of the jaw.

Denosumab also is approved at a lower dose to treat osteoporosis, but under the brand name Prolia.

Asthmatx's Alair (bronchial thermoplasty) – reduces need for controller medications

At the American College of Allergy, Asthma, and Immunology, researchers reported on a retrospective study which found that asthma patients who have undergone bronchial thermoplasty, an endoscopic procedure in which heat energy is applied to the walls of the airways to widen them and limit their ability to constrict, can safely stop one of their controller medications. The AIR trial looked at 109 patients with stable asthma on a combination of long-acting beta agonists and inhaled corticosteroids, randomizing them to thermoplasty or medical management.

The study found statistically significant benefits in patients undergoing thermoplasty:

- Greater morning peak expiratory flow, both at the end of the treatment and at one year vs. decreases with control.
- Less rescue medication than controls at each time point.
- ≤25% increase in symptom-free days vs. decreases with control.
- Total symptom score decrease vs. an increase for control.
- Better asthma control vs. control.
- Better quality of life vs. increases among controls.

The results suggest that it's possible to withdraw the long-acting beta agonist, a researcher said.

Automated external defibrillators (AEDs) – subject of increased FDA scrutiny

The FDA will hold a public meeting on December 15-16, 2010, to discuss with industry and other external parties ways to improve these devices. The FDA wants to:

- Share its understanding of the risks and benefits of external defibrillators.
- Clarify its current expectations for how industry should identify, report, and take action on problems observed with these devices.
- Promote innovation for next-generation devices to bring safer, more effective external defibrillators to market. The FDA is encouraging design and manufacturing improvements.

The FDA is calling on AED manufacturers "to fix long-standing problems with the emergency devices that have triggered dozens of recalls and occasionally have led to injuries and death." The FDA said the devices have been "plagued by design and manufacturing flaws for years, occasionally failing to work in life-and-death situations" and complained that manufacturers have failed to fix problems that led to the recall of hundreds of thousands of devices.

About 200,000 AEDs – made by Philips Healthcare, Cardiac Science, and other companies – are sold annually, and ~1 million are estimated to be in use. However, in the last five years there have been 68 recalls, and the FDA has received more than 28,000 reports of AEDs failing.

BAUSCH + LOMB – no more "no rub"

B+L is changing the directions for use of all of its multipurpose contact lens solutions worldwide. The label will no longer say "no rub." Instead, it will recommend customers use a "rub and rinse" regimen. The change was not mandated by the FDA; rather, the company chose to "proactively change our… labeling to only include a rub regimen for cleaning and disinfecting lenses." The change is being transitioned in and will be completed for all solutions by May 2011.

BRISTOL-MYERS SQUIBB and PFIZER's apixaban – Phase III trial halted for safety

The data safety monitoring board (DSMB) ordered a halt to the Phase III APPRAISE-2 trial of this Factor Xa inhibitor (anti-coagulant) in high-risk acute coronary syndrome (ACS) patients. The company reported "clear evidence of a clinically important increase in bleeding among patients randomized to apixaban. This increase in bleeding was not offset by clinically meaningful reductions in ischemic events."

APPRAISE-2 was an ~11,000-patient trial of apixaban 5 mg BID vs. placebo in 40 countries, and the DSMB made it clear that the study discontinuation applies only to that trial. The companies plan to continue to investigate apixaban in other indications, including venous thrombolic events (VTEs) and atrial fibrillation, where the drug has demonstrated "promising" results.

CEPTION THERAPEUTICS' reslizumab – suggestion of benefit in severe asthma

This humanized anti-IL-5 monoclonal antibody failed to show any statistically significant improvement in lung function and asthma control in a Phase II study of >100 patients with eosinophilic airway inflammation, a subtype of severe asthma. However, the researchers, who reported the results at the American College of Allergy, Asthma, and Immunology (ACAAI) meeting in Phoenix, were encouraged with the results, saying they showed a trend to improvement in both measures.

COPD – may be an autoimmunity problem

Spanish researchers suggested in an article in the American Thoracic Society's ***American Journal of Respiratory and Critical Care Medicine*** that moderate-to-severe chronic obstructive pulmonary disease (COPD) may be an auto-immunity problem. After studying autoantibodies in 328 COPD patients and comparing them to 67 healthy controls, they found that 34% of COPD patients had up to 11-fold more autoantibodies circulating in their blood than controls.

An investigator said, "We can only speculate on the mechanisms underlying the observed associations. The prevalence of [the antibodies] may be non-specific markers of an ongoing autoimmune response or may be directly involved in the pathogenesis of the disease. However, these alternatives are not mutually exclusive…It raises the possibility of future clinical trials evaluating possible new therapies for this disease, for instance, immunomodulators."

EORTC-NCI-AACR Molecular Targets and Cancer Therapeutics Symposium in Berlin – review of some interesting findings

- **ACCELERON's ACE-041, an ALK-1 inhibitor –** A Phase I, first-in-man, ascending-dose trial showed that this drug, injected subcutaneously once every three weeks, is safe and effective in patients with advanced cancers and, in some cases, halted disease progression. Side effects included mild-to-moderate peripheral edema, fatigue, nausea, headache, anorexia, and anemia. One case of Grade 3 congestive heart failure (CHF) also was reported. One patient with refractory head and neck cancer achieved a partial response, and three patients had prolonged disease stabilization. An expanded cohort study is ongoing at the dose level intended for Phase II studies.
- **Blood-brain barrier breach –** German researchers have developed a way of smuggling an anti-cancer drug past the protective blood-brain barrier and into brain tumors and metastases using a Trojan Horse – a nanocarrier.
- **Cough medicine –** may help doctors identify how breast cancer patients metabolize tamoxifen. Researchers found that cough syrup may be able to be used as a probe to enable doctors to identify patients with altered metabolism, then use that information to improve individual treatment, making it more effective and reducing the chances of side effects.
- **EXELIXIS' XL-184 –** showed some "intriguing effectiveness" in treating bone metastases. In early testing, 19 of 20 patients showed an improvement in the scans used to determine whether cancer has metastasized to the bone.
- **HYBRIGENICS' inecalcitol –** A Phase IIa trial of this anti-cancer drug targeting vitamin D receptors on cancer cells showed "encouraging" results in hormone resistant prostate cancer patients, lowering PSA.
- **MERCK's MK-4827, a PARP inhibitor –** showed anti-tumor activity in a Phase I trial in a range of solid tumors.
- **THRESHOLD PHARMACEUTICALS' TH-302 –** Two positive trials of this hypoxia-activated prodrug were reported.
  - The 3-arm, multicenter, dose-escalation Phase I/II **402 trial** in combination with Lilly's Gemzar (gemcitabine), docetaxel, or pemetrexed in patients found 1 complete response in pancreatic cancer (5%) as well as 23%-26% partial response in several solid tumors. In addition, progression-free survival (PFS) ranged from 4.2 months to 6.4 months when TH-302 was combined with Gemzar, and among the 15 patients with castrate-resistant prostate cancer (CRPC), 73% had a PSA decline of ≥50%.
  - The **403 trial** in combination with doxorubicin found a partial response in 33% and a PFS of 6.4 months in patients with advanced soft tissue sarcoma.

  Overall, hematologic toxicity was "acceptable," and skin and mucosal toxicities were described as "well managed at current dose levels." A pivotal, randomized trial of TH-302 + Gemzar is underway in pancreatic cancer, and results are expected in 2011.

Flu and RSV – new diagnostic test developed

A new, fully automated test has been developed to quickly and accurately diagnose influenza A and B as well as respiratory syncytial virus (RSV) A and B. The study on the new test, "Respiratory Virus Nucleic Acid Test SP" (RVNATsp), was reported in the ***Journal of Clinical Microbiology***. Principal investigator Nathan Ledeboer, PhD, of the Medical College of Wisconsin said, "Instead of relying on insensitive but rapid influenza tests for diagnosis in the clinic, or waiting 24 hours or more for molecular results to come back, we can now provide molecular level sensitivity in less than three hours."

In the study, the microarray assay, which was tested on 720 patient samples collected throughout the U.S., was 98% sensitive and 96% specific. By comparison, the conventional alternative, culture, is nearly 100% specific but only 70% sensitive.

Genetic colorectal testing – cost-effective

Widespread genetic testing for Lynch Syndrome appears to be a cost-effective strategy for identifying those at risk for colorectal and endometrial cancer, according to a report in ***Cancer Prevention Research***, a journal of the American Association for Cancer Research (AACR). Dr. Stephen Gruber of the University of Michigan, a lead investigator in the study, said, "Genetic testing was always assumed to be cost-effective for those at high risk based on their family history, but this shows it would be cost-effective in a wider population, similar to the cost-effectiveness of mammography."

Using a mathematical risk model developed by Archimedes, followed by genetic testing for those who had risk >5%, colorectal cancers could be reduced by 12.4% and endometrial cancers by 8.8%. The average cost-effectiveness ratio, $26,000, is well below the benchmark of $50,000 for quality-adjusted life year (QALY) saved.

AACR president-elect Dr. Judy Garber from the Dana-Farber Cancer Institute said, "This will affect a wide population by changing our thinking about risk for colon cancer. Young individuals will be able to have an assessment of their personal and family history using a computerized model that can help guide their colon cancer risk management for decades and make it possible to prevent significant numbers of colon and associated cancers, especially in young people, for a very reasonable cost. It is a huge step forward in terms of bringing the benefits of cancer genetics to the broader population using tests that have, in the past, been considered too expensive."

Infusion pumps – more of the never ending recalls

This week's infusion pump recall is Sigma's Spectrum Model 35700, which the FDA said may fail suddenly, causing inaccurate flow conditions during use, ranging from back flow to over-infusion, including free flow. The pump does not issue an alarm when this occurs. The FDA said the result could be serious injury or death. Healthcare facilities are being asked to verify by serial number if their pumps are part of the recall and return affected devices.

Needleless pre-filled glass syringes – compatibility problems with IV access systems

The FDA warned healthcare professionals, especially those working in emergency and critical care settings, about compatibility problems when certain needleless pre-filled glass syringes are used with some needleless intravenous (IV) access systems. The syringes may malfunction, break, or become clogged when they are being connected to a needleless IV access system.

Most of the adverse event reports related syringes containing adenosine, marketed by Teva, Sagent, Baxter, and Wockhardt. Adenosine must be injected rapidly into the blood stream in emergency situations, and this failure could delay treatment, the FDA emphasized. There have also been reports of problems related to some pre-filled needleless glass syringes containing amiodarone.

In some cases, when an attempt is made to connect to pin-activated needleless IV access systems, the syringe may cause the pin to break, clogging the syringe or damaging the IV tubing and/or the needleless connector and requiring reestablishment of a new IV access. These failures can cause a delay in administration of the medication, which could potentially result in serious harm to patients.

The FDA is advising healthcare organizations currently using glass pre-filled syringes to consider stocking adenosine supplied in vials or pre-filled plastic syringes as a back up measure.

The FDA also expanded the scope of its review to include all currently marketed pre-filled needleless glass syringes intended for use with needleless IV access systems, where delay in administration could potentially result in a life-threatening event. The FDA is working with manufacturers to correct the problem and identify additional mitigation strategies.

The FDA is encouraging healthcare professionals and healthcare organization managers to report adverse events or problems experienced with the use of needleless pre-filled glass syringes. The Agency is particularly interested in any description of the

nature of the syringe failure, any adverse patient outcomes, and any mitigation strategies that have been identified or implemented by users of these products.

Pharma drug discovery – not very productive

An analysis of FDA drug approvals in the journal ***Nature Reviews Drug Discovery*** reported that of the 252 new drugs approved by the FDA between 1997 and 2008:

- Pharmas discovered only slightly more than half of the new drugs, fewer than half the novel drugs, and about half of the priority review drugs.
- Universities discovered a quarter of the new drugs and more than a quarter of the orphan drugs.
- Biotech discovered the fewest new drugs, but 80% of all their drugs got priority review.

252 FDA Drug Approvals 1997-2008

Measurement	Pharmas	Biotech	Universities
Discovery	58%	18%	24%
Priority review (n=123 or 49%)	46%	30%	23%
Novel mechanisms/ chemical structures (n=118 or 47%)	44%	25%	31%
Orphan drugs (n=88 or 35%)	~72%		~28%

PFIZER

- **Axitinib – positive Phase III results in metastatic renal cancer.** Pfizer reported positive top line results from the Phase III AXIS trial and plans to present the full data at an upcoming medical meeting. The company said axitinib met the primary endpoint, showing significant improvement in PFS vs. Pfizer's Sutent (sunitinib). The adverse event profile was described as "generally manageable."

  A Pfizer official said, "These results provide insight into the potential value of axitinib as part of a sequential treatment approach in patients with advanced RCC (renal cell carcinoma). We will work with health authorities to determine possible filing options for axitinib for use in patients with advanced RCC." Annually, ~210,000 people worldwide are diagnosed with RCC, with nearly 102,000 dying. Five-year survival rates for patients with advanced RCC remain low (~20%).

- **BeneFix (nonacog alfa, coagulation Factor IX) – new formulation is safer.** A 7-year European registry of 218 hemophilia B patients treated with BeneFix found that the reformulated version of the drug was associated with fewer adverse events than the original formulation. Pfizer researchers said serious adverse events occurred in 24.7% of patients on the older formulation vs. none with the reformulated version, which was introduced in 2007 to minimize agglutination of red blood cells in the syringe or tubing used to administer it.

XANODYNE PHARMACEUTICALS' Darvon (propoxyphene) and Darvocet (propoxyphene + acetaminophen) – FDA orders propoxyphene off the market

At the FDA's request Xanodyne Pharmaceuticals is voluntarily withdrawing Darvon and Darvocet from the U.S. market. The FDA also has asked (read: ordered) generic manufacturers of this opioid to cease sales of their propoxyphene-containing products.

This action comes after a multiple ascending-dose study that Xanodyne did in preparation for an FDA-mandated post-marketing safety study found the drug, at the maximum approved dose, caused cardiac rhythm abnormalities in healthy volunteers. It is believed to be the first time the FDA has ordered a drug withdrawal based on a postmarketing study mandated under new authorities granted by the FDAAA (Food and Drug Administration Amendments Act) of 2007.

Dr. John Jenkins, director of the FDA's Office of New Drugs, Center for Drug Evaluation and Research (CDER), said, "These new heart data significantly alter propoxyphene's risk:benefit profile. The drug's effectiveness in reducing pain is no longer enough to outweigh the drug's serious potential heart risks."

Dr. Jenkins added that QT changes like this have been linked to serious adverse effects, including sudden death. The FDA is advising healthcare professionals to stop prescribing propoxyphene to their patients and is telling patients who are currently taking the drug to contact their healthcare professional as soon as possible to discuss switching to another pain management therapy. However, Dr. Gerald Dal Pan, director of the FDA's Office of Surveillance and Epidemiology, CDER, said long-term users are not at greater cardiac risk; the effects are not cumulative, and once patients stop taking the drug, the risk goes away.

Propoxyphene was first approved by the FDA in 1957. At that time QT studies were not required before a drug was approved. Since 1978, the FDA received two requests to remove propoxyphene from the market, and it rejected both of those, concluding until now that the benefits outweighed the safety risks.

- 1978 – Public Citizen filed a Citizen Petition requesting withdrawal of propoxyphene from the market, and the FDA rejected that petition.
- 2005 – The U.K. began a phased two-year withdrawal of propoxyphene products.
- 2006 – Public Citizen again petitioned the FDA to withdraw propoxyphene.
- 2008 – Public Citizen sued the FDA to force a response to its 2006 Citizen Petition.
- January 2009 – An FDA advisory committee voted 14 to 12 against the continued marketing of propoxyphene products, noting that additional information about the drug's cardiac effects would be relevant in weighing its risks and benefits.
- June 2009 – The European Medicines Agency (EMA) started a phased withdrawal of propoxyphene.
- July 2009 – The FDA rejected the second Citizen Petition but did add a new boxed warning and a new Medication Guide to the propoxyphene products. The FDA also ordered Xanodyne to conduct a cardiac safety study.

The cardiac safety study was never initiated because the Xanodyne ascending-dose study done to determine a safe dose for the cardiac safety study found such serious rhythm problems that it became the basis for the FDA's decision to withdraw all propoxyphene products. Dr. Jenkins said, "The multiple ascending-dose study was conducted using the same monitoring they would use for a thorough QT study. They started with 600 mg/day, which is the maximum recommended dose…and studied that to steady state [for several days] in volunteers. At that dose, the maximum corrected QT change was ~30 ms vs. placebo. They then went to a 900 mg dose, which is a 50% increase above the maximum recommended dose, and there the maximum change in QT was 38 ms. I do not believe there were any subjects with QT >500 ms, a threshold sometimes used in the studies, but the changes exceeded the 20 ms threshold in ICH guidance. There were also increase in PR and a widening of the QRS complex at both doses and in a dose-related fashion."

What was particularly concerning to the FDA was that the effects occurred in healthy volunteers at approved doses. The FDA has known for a long time that opioids, including propoxyphene, can be dangerous when overdosed or in patients who are dehydrated, have decreased kidney function, etc. Dr. Jenkins said, "[The findings in healthy volunteers] suggested that the heart risk of propoxyphene could apply to all users and not just those who took excessive doses or those who had conditions that might [make them more susceptible]… Since it is not possible to accurately predict which patients might be at risk or to monitor patients on the drug for signs of an increased risk, we determined a REMS (risk evaluation and mitigation strategy) would not be appropriate in this case. Therefore, we decided the drug should no longer be available."

In 2009, ~10 million Americans took a propoxyphene product, most commonly Darvocet (or a generic version of Darvocet). The FDA could not say how many people have died from cardiac problems related to propoxyphene products, but they said that the adjusted death numbers are "consistently higher" for propoxyphene than for tramadol (Johnson & Johnson's Ultram and its generics) or hydrocodone. Dr. Jenkins said, "Propoxyphene is an opioid, and it has always been known that overdoses of opioids, like morphine, can lead to death. There have long been reports of overdose deaths. What is unique here is the new heart data show the adverse effects on the electrical activity of the heart occur at normal doses and in healthy people, not just with overdoses."

Asked how this action will impact other products approved a long time ago and whether they will now have to do QT studies, Dr. Jenkins said, "Clearly, drugs approved before modern standards were in place may have some of these safety concerns, but generally those would be identified through other mechanisms…such as adverse event reports and epidemiologic studies. In the case of propoxyphene, we didn't just randomly ask for a thorough QT study. There were a lot of signals of concern about cardiotoxicity…We requested [a QT] study based on knowledge from other sources…and that is how we will apply it to other older drugs. If we see a signal of concern, we can order additional safety studies under FDAAA."

Asked if the FDA will now consider restriction of Purdue Pharma's OxyContin (oxycodone) to only severe pain and not moderate pain patients, Dr. Jenkins said no, "We are very aware of the safety concerns related to OxyContin. We've had several public meetings and discussions. We are in the process of developing a REMS for OxyContin and other similar extended-release and long-acting opioids. We are aware of the questions related to restriction of OxyContin to only severe pain, but we currently believe the product is safe and effective when used as directed in the approved labeling, which does include moderate-to-severe pain."

Dr. Sidney Wolfe, director of Public Citizen's Health Research Group, is now calling for a congressional investigation into who at the FDA, specifically within CDER, "was responsible for the loss of so many lives in this country. It is clear that long before today, many drug safety experts in the Office of Surveillance and Epidemiology had decided the drug should be removed from the market."

Dr. Wolfe called the Agency's failure to act sooner "a serious indictment of the FDA's long-lasting unwillingness to protect people in this country from a deadly but barely effective painkiller…Due to FDA negligence, at least 1,000 to 2,000 or more people in the U.S. have died from using propoxyphene since the U.K. ban was announced…From 2005 through 2009, in Florida alone, 395 deaths were 'caused' by propoxyphene. If data from 2007 are representative, in that year, 78% of the Florida deaths caused by propoxyphene were ruled accidental."

He noted that in a study on dogs published 31 years ago, Lilly researchers, who discovered propoxyphene, stated, "Cardiac conduction depression may be a factor in some of the [human] cardiac toxicities associated with propoxyphene overdose." Dr. Wolfe added, "This study examined the same kind of function measured in the human study now being put forth by the FDA as a justification for belatedly banning propoxyphene."

REGULATORY NEWS

FDA reclassifies negative pressure wound therapy devices

Effective December 17, 2010, the FDA will reclassify non-powered suction apparatus devices intended for negative pressure wound therapy as Class II (special controls) "in order to provide a reasonable assurance of safety and effectiveness of the device. The FDA also issued a new guidance document for their development.

The FDA said it identified several health risks associated specifically with these devices that must be addressed by any company submitting a 510(k) application, but the company will only need to show that its device meets the recommendations of the guidance or in some other way provides equivalent assurance of safety and effectiveness. Those issues include:

- Adverse tissue.
- Material degradation.
  - Improper function of suction apparatus (e.g., reflux of waste exudates to wound, incorrect delivery of negative pressure).
  - Non-compatibility with other therapeutics and diagnostics (e.g., MRI, hyperbaric chamber, defibrillation).
- Uncontrolled transmission of infectious agents.
- Unsafe use of device (e.g., improper wound selection, improper wound management, improper placement).

Is the FDA complying with the court order on Plan B?

A reproductive rights group has accused the FDA of being in contempt of court for failing to respond to a judge's order to reconsider restrictions on the controversial morning-after pill Plan B. In March 2010, a judge ordered the FDA to reconsider its 2006 decision to only allow women aged ≥18 to buy Plan B without a prescription. The FDA said the best way for the Agency to comply with the court's order is to review a supplemental drug application expected to be submitted by Plan B's manufacturer.

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 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 Xgeva (denosumab), and Eisai's Halaven (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	**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 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
	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	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