Trends-in-Medicine

Quick Takes

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September 26, 2010

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

SHORT TAKES

- **ABBOTT LABORATORIES** and **REATA PHARMACEUTICALS** will jointly develop and market bardoxolone methyl to treat chronic kidney disease. The drug, an oral antioxidant inflammation modulator, was found to improve kidney function in patients with chronic kidney disease and Type 2 diabetes. Phase III trials are expected to start by 2011.
- **ACTELION PHARMACEUTICALS** was subpoenaed by the U.S. Attorney's Office for the Northern District of California, which was seeking documents relating to the U.S. marketing and sales practices of Actelion's Tracleer (bosentan), a drug used for the treatment of patients with pulmonary arterial hypertension.
- **ALLERGAN's Lap-Band**, an adjustable gastric banding system, will be reviewed by the FDA's Gastroenterology and Urology Devices Advisory Committee on December 3, 2010. Allergan is requesting an expanded indication for use to include weight reduction in patients with a body mass index (BMI) of ≥35 kg/m^2 or a BMI ≥30 kg/m^2 with one or more comorbid conditions.
- **AMGEN's Aranesp (darbepoetin alfa)** will be reviewed again by the FDA's Cardiovascular and Renal Drugs Advisory Committee on October 18, 2010, so the panel can consider the results and analyses of the TREAT trial. The meeting is a follow-up to a September 2007 advisory committee meeting at which the panel discussed updated information on the risks and benefits of erythropoiesis-stimulating agents used in the treatment of anemia due to chronic kidney failure.
- **AMGEN's Epogen** and **Johnson & Johnson's Procrit** (which is made by Amgen) – Certain lots of these anemia treatments were recalled as a precaution because the vials may contain extremely thin glass flakes (lamellae) that are barely visible. The potential serious adverse events resulting from the IV use of a sterile injectable product with particulates include embolic, thrombotic, and other vascular events (e.g., phlebitis), and subcutaneous administration could result in foreign body granuloma, local injection site reactions, and increased immunogenicity.

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- **ASTRAZENECA's vandetanib**, an experimental thyroid cancer drug, was filed for regulatory approval with the FDA and with the European Medicines Agency (EMA). The company pulled its application last year for vandetanib to treat lung cancer, following disappointing clinical data. The current submissions are based on study results that were presented at the American Society of Clinical Oncology (ASCO) meeting in June 2010. The FDA granted priority review.

- **BOEHRINGER INGELHEIM's Pradaxa (dabigatran) –** An FDA panel unanimously recommended approval of Pradaxa, a blood thinner, for reducing the risk of stroke in patients with atrial fibrillation. A final decision is expected by October 19, 2010.

- **BOSTON SCIENTIFIC** signed a merger agreement to acquire **Asthmatx**, which designs, manufactures, and markets a less-invasive, catheter-based bronchial thermoplasty procedure for the treatment of severe persistent asthma, the Alair Bronchial Thermoplasty System, which received FDA approval in April 2010.

- **BRISTOL-MYERS SQUIBB** plans to cut ~3% of its 28,000 employees to reduce costs.

- **CATALYST PHARMACEUTICAL PARTNERS' CPP-115**, a novel GABA aminotransferase inhibitor, was granted orphan drug designation by the FDA for the treatment of infantile spasms (West Syndrome). The company is conducting non-clinical safety and efficacy studies and expects to file an IND in the first half of 2011.

- **ENDO PHARMACEUTICALS' tamper-resistant Opana ER (oxymorphone)** was granted FDA priority review. This new formulation, which was developed by Grünenthal, is crush-resistant and forms a sticky gel in water. However, it is still susceptible to chewing. The PDUFA date is January 7, 2011.

- **EVOTEC AG** entered into a collaboration with **Almirall** to identify small molecule modulators of an ion channel target involved in respiratory diseases. Evotec will apply its electrophysiology and ion channel pharmacology expertise as well as its state-of-the art screening platform for the identification and validation of novel modulators of the selected ion channel.

- **GEN-PROBE's Progensa PCA3 assay –** The company submitted a Premarket Approval Application (PMA) to the FDA for this assay to screen urine samples for a gene linked to prostate cancer. The test is designed for patients who have had a negative biopsy to help determine if another biopsy is needed. The FDA has advised the company that an advisory committee meeting will be required, but no date for the meeting has been set.

- **GLAXOSMITHKLINE** sued **Roche** and its Genentech unit, accusing them of infringing on a production-related patent for the cancer drug Herceptin (trastuzumab). GSK said the infringement stems from "making and/or having made therapeutic antibody products, including without limitation Herceptin."

- **GLAXOSMITHKLINE's Avandia (rosiglitazone) –** U.S. and European regulators came to the same conclusion – that there is a signal for cardiovascular risk with Avandia, but they took very different actions. The FDA plans to restrict access to the drug by imposing a risk evaluation and mitigation strategy (REMS) that limits who can get the drug, requires physicians to document patient eligibility for the drug as a second-line agent only, and requires patients to sign a document that they understand the risks. The EMA plans to remove Avandia from the market. However, both actions won't go into effect for months!

- **GLAXOSMITHKLINE's Rotarix (rotavirus oral vaccine) –** Based on preliminary data from a Mexican postmarketing study involving infants <1 year old, the FDA warned that Rotarix may increase the risk of bowel obstruction. An increased number of cases occurred in the 31 days following the first dose of the vaccine and primarily within seven days. According to the FDA, additional information has been added to the Warning and Precautions labeling of the vaccine to inform healthcare providers about the preliminary results.

- **HOLOGIC's Selenia Dimensions 3-D tomosynthesis system –** The FDA's Radiologic Devices Advisory Committee voted that the benefits outweigh the risks of this digital breast diagnostic system, and the committee voted unanimously that it is safe and effective. Selenia already has a CE Mark and is sold in Europe. If the FDA approves Selenia, it would be the first tomosynthesis system on the U.S. market.

- **HOSPIRA's Symbiq One- and Two-Channel infusion pumps** were the subject of a second Class I recall by the FDA. The recall was prompted because unrestricted flow of fluid or medication can occur if an administration-set cassette is improperly removed. The FDA noted that if this happened, it could result in life-threatening effects and injuries, especially in critically ill patients, patients with congestive heart failure, and neonates.

- **LASIK vision correction –** The FDA has started an investigation of the safety of this common eye surgery. Morris Waxler, PhD, a former FDA official who helped get LASIK approved in the 1990s, later spoke out against the procedure and now has filed a Citizens Petition urging the FDA to take steps to stop what he called "the epidemic of permanent vision problems caused by LASIK." According to Dr. Waxler's analysis of FDA data, half of LASIK patients experience side effects and more than a third continue to need glasses or contacts.

- **MERCK KgaA's cladribine –** European regulators rejected this oral multiple sclerosis drug, saying the

benefits don't outweigh the risks. The EMA raised concerns about four cancer cases observed during clinical trials and about the drug's dampening of the immune system. The FDA has given cladribine priority review status and may rule on the drug late this year.

- **NOVARTIS's Gilenya (fingolimod)** was approved by the FDA as a first-line treatment for relapsing forms of multiple sclerosis, making it the first oral treatment in the U.S. for the disease.

- **NOVARTIS's Miochol-E (acetylcholine chloride intraocular solution)** was sold to **Bausch + Lomb** in order to comply with anti-trust requirements of the Federal Trade Commission as part of its acquisition of Alcon. Under the agreement, Novartis will provide technical manufacturing assistance during the transfer of Miochol-E.

- **OCEANA THERAPEUTICS' Solesta**, a potential treatment for fecal incontinence in patients who have failed conservative therapy, will be reviewed by the FDA's Gastroenterology and Urology Devices Advisory Committee on December 2, 2010.

- **OCTAPHARMA's Octagam –** The company initiated a voluntary withdrawal of ***all*** lots of Octagam currently in the U.S. market. The company and FDA agreed that until a root cause of the previously reported thromboembolic events can be determined and the problem corrected, the most prudent course of action was to suspend further administration of Octagam.

- **OPTIMER PHARMACEUTICALS' fidaxomicin** was submitted to the FDA for use in treating *Clostridium difficile* (*C. diff*), a potentially fatal bacterial infection of the colon. The company requested priority review, and if that is granted, regulators could make a decision by mid-2011.

- **Retina surgeons** generally offer financial aid or social services to patients who need assistance to treat an eye problem. In a survey by ***Retina Today***, 89% of retinal surgeons said they offer these services.

- **SOLTA MEDICAL** received FDA clearance for its Fraxel re:store dual laser system for skin resurfacing designed to treat actinic keratosis, a pre-malignant skin growth caused by sun damage. The company also announced that chief technology officer Leonard DeBenedictis will retire from the company and its board of directors effective October 1, 2010.

- **ZIOPHARM ONCOLOGY's Zinapar (darinaparsin)** was granted orphan drug status by the FDA as a potential treatment for peripheral T-cell lymphoma, which represents about 10%-15% of the estimated new cases of non-Hodgkin's lymphoma diagnosed each year.

NEWS IN BRIEF

Alzheimer's disease (AD) – a possible new drug target

Scientists at the Gladstone Institute of Neurological Disease reported in the journal ***Neuron*** on a new approach to reducing toxic proteins in AD and other neurodegenerative diseases which ***might*** lead to new treatments for these diseases – measuring levels of an enzyme called SIRT1 which is reduced in AD brains. The reduction in SIRT1 is associated with tau acetylation and aggregation. The researchers found that patients with early and moderate AD had elevated levels of tau acetylation and inhibiting SIRT1 increased levels of both the acetylated tau and the p-tau in neurons grown in culture dishes.

The researchers have already identified a small molecule compound that eliminates toxic p-tau in neurons that might represent a new class of anti-AD drugs.

ATHERSYS' MultiStem – moves a step closer to reality

MultiStem, a multipotent adult progenitor stem cell therapy, was granted orphan drug status by the FDA for the prevention of graft vs. host disease. A study published in ***Experimental Neurology*** demonstrated that intravenous injection of MultiStem provides neurovascular protection after traumatic brain injury in an established preclinical model of brain injury. The article outlines how the administration of MultiStem preserved the blood brain barrier and reduced the effects and extent of the brain injury. Dr. Charles Cox, director of the Pediatric Trauma Program at the University of Texas Medical School at Houston and co-author of the study, said, "Our results indicate that multipotent adult progenitor cells could provide multiple benefits in the context of neurological injury."

Atrial fibrillation ablation – surgery may be better for patients <age 45

According to a study published in ***Circulation: Arrhythmia and Electrophysiology***, young patients with atrial fibrillation tend to be more symptomatic and less willing to take long-term medications, yet catheter ablation remains recommended as second-line therapy, regardless of age. The researchers examined the medical records of 1,548 patients who underwent catheter ablation and found that a year after surgery, 87% of the patients <age 45 had experienced little or no atrial fibrillation. The researchers concluded that it may be appropriate to consider ablative therapy as first-line therapy in this age group.

Atypical antipsychotics – linked to VTEs

A retrospective study by British researchers that was published in the ***British Medical Journal*** found that atypical antipsychotic drugs were associated with increased rates of venous thromboembolism (VTE). They also found that VTEs

were more common in patients who: used any antipsychotic drug in the past two years (odds ratio 1.32), used a first-generation antipsychotic (OR 1.28), started antipsychotic therapy in the past three months (OR 1.97), used either a high potency (OR 1.28) or low potency (OR 1.99) drug, or that were injected (OR 3.24).

"If other studies replicate these findings, antipsychotic drugs should be used more cautiously for nausea and agitation, etc., especially among patients at high risk of thromboembolism," the researchers concluded after studying 25,532 cases of VTE in Great Britain's primary care database, along with 89,491 patients without VTE matched to the cases by age, sex, and location. Patients on warfarin or without records for ≥2 years were excluded.

Johnson & Johnson's Risperdal (risperidone) was not significantly associated with VTE risk (OR 1.24), but AstraZeneca's Seroquel (quetiapine) had a strong association (OR 2.81).

However, the estimated number-needed-to-harm (NNH) was 722 for haloperidol and 467 for Seroquel overall, but lower for patients age ≥65.

In an accompanying editorial, two Italian researchers noted that there is some mechanistic reason to believe there could be an association between atypical antipsychotics and VTE. They said that earlier research found that some antipsychotic drugs can boost platelet aggregation or responsiveness to procoagulant factors. However, they also pointed out that the VTE risk could be due to the psychiatric condition rather than treatment choices could not be excluded.

Cardialysis and Sticares InterACT – combining on drug development consulting services

Cardialysis and Sticares InterACT, two Dutch contract research organizations (CROs), have entered into a strategic collaboration to provide drug development consulting services in the field of cardiovascular and metabolic medicine. Cardialysis is known for its laboratory techniques, statistics, data management, and clinical trial management; Sticares InterACT is known for clinical project management, site management (in 26 countries, especially Eastern Europe), medical monitoring, and pharmacovigilance.

The collaboration between Cardialysis and Sticares InterACT ensures high quality clinical research services, accelerated subject recruitment, therapeutic competence, and medical expertise for current and future clients. Cardialysis and Sticares InterACT together offer a complete spectrum of services from pre-clinical consulting to planning, managing, executing, and reporting Phase II-IV research programs.

Chelsea Therapeutics' Northera (droxidopa) – positive preliminary Phase III results

Preliminary analyses of a Phase III study showed clinically meaningful and statistically significant improvement in symptoms associated with neurogenic orthostatic hypotension. The multinational, double-blind, placebo-controlled, randomized study evaluated symptomatic and functional improvements using the orthostatic hypotension questionnaire, a two-part questionnaire that uses an 11-point scale (zero to 10) to assess the severity of six symptoms and four patient function criteria.

The design consisted of an initial open-label dose titration, followed by a 7-day open-label washout period prior to a 7-day treatment period. During the open-label dose titration period, all patients were titrated to an optimal therapeutic dose of Northera and were required to demonstrate both a blood pressure and symptomatic improvement to be eligible for the blinded study. This was followed by another 7-day washout period, after which patients were randomized to either placebo (n=79) or Northera treatment (n=81) for one week. Northera proved to be safe and effective. Northera patients experienced a mean increase of 11.2 mmHg after one week of treatment, compared to a mean change of 3.9 mmHg in standing systolic blood pressure for those receiving placebo.

Edwards Lifesciences' Sapien – positive results

The results of the PARTNER trial of this transfemoral percutaneous aortic valve were published in the ***New England Journal of Medicine (NEJM)*** and presented at TCT. The valve met both primary endpoints – beating standard care (which included balloon aortic valvuloplasty) on all-cause mortality and the composite of all-cause mortality and repeat hospitalization at one year. The delta between transcatheter aortic valve implant (TAVI) and standard care was ~20% on both. In addition, TAVI patients had statistically significantly lower death from CV causes and fewer cardiac symptoms at one year.

The number needed to treat (NNT) to prevent 1 death was 5, and the NNT to prevent 1 death or repeat hospitalization was 3. Interestingly, most Kaplan-Meier curves showed dramatic differences between the two therapies, beginning at about one month and widening over time. On Forest plots all but one subgroup – regardless of age, gender, BMI, STS score, LVEF, pulmonary hypertension, degree of mitral regurgitation, COPD, and prior CABG or PCI – favored TAVI. Only patients with peripheral vascular disease did not clearly favor TAVI, but in that case the type of therapy was neutral, favoring neither approach.

ENDO PHARMACEUTICALS' PRO2000 – failed in a Phase III trial

In a randomized, double-blind, parallel-group Phase III trial at 13 clinics in South Africa, Tanzania, Uganda, and Zambia, researchers tested the efficacy of 2% and 0.5% PRO2000 vaginal gel in the prevention of HIV-1 transmission. The gel was found to be safe but ineffective, despite promising animal studies and early clinical trials. The trial, which was published in ***The Lancet***, found the incidence of HIV was almost the same in treated women as with placebo.

In an accompanying commentary, Dr. Sandra McCoy of the University of California, Berkeley, and colleagues said the report "will certainly indicate the end of the road for PRO2000 as a potential HIV-prevention tool for women."

e-prescribing – increasing but still low numbers using it

Roughly one in three office-based doctors now uses e-prescribing. That's 200,000 doctors vs. 156,000 at the end of 2009 and only 74,000 at the end of 2008. Surescripts, which operates the largest U.S. electronic prescribing network, said 47 states more than doubled their use of electronic prescribing last year. In 2009, Congress authorized funding to promote electronic health records (EHRs) as part of the economic stimulus package. Incentives will be paid out over five years, and by 2015 providers will face penalties if they don't adopt the new technology.

GLAXOSMITHKLINE's Arixtra (fondaparinux) – effective, but expensive

Researchers conducted a randomized, double-blind, 45-day trial of 3,002 patients with superficial-vein thrombosis of the legs, assigned to receive either subcutaneous Arixtra 2.5 mg QD or placebo. The study, which was published in the ***New England Journal of Medicine***, found the treatment to be safe and effective.

In an accompanying editorial, Dr. Lee Goldman of Columbia University and Dr. Jeffrey Ginsberg of McMaster University in Canada challenged the findings, not for their science but because of the cost of the treatment, which can range from $2,124 to $7,380 in New York City for a 45-day supply.

Intravenous aspirin – effective for medication withdrawal headaches

Patients hospitalized for severe headache caused by medication withdrawal can be treated safely and effectively with intravenous aspirin. That was the finding of an 86-patient study published in the journal ***Neurology***. More than 25% of the time, people experienced a ≥3-point reduction in pain scores, on a 10-point rating scale, following IV aspirin. Side effects were mild and included nausea, vomiting, and pain from IV insertion.

Principal investigator Dr. Peter Goadsby of the University of California, San Francisco, said, "It's important to note that participants knew they were getting treatment and a placebo was not used…Our findings warrant more research into the use of IV aspirin for severe headache or migraine."

Mammography – perhaps not as effective as believed

A study published in the ***New England Journal of Medicine*** may reignite the controversy about how often and which women should be screened for breast cancer with mammograms. In the study, Norwegian researchers found that routine mammogram screening was less effective at preventing cancer deaths than expected. The breast cancer death rate dropped 10% among women aged 50-69 who were offered routine mammograms and expert follow-up, but it dropped 8% in women over age 70 who were not urged to have routine mammograms.

In an accompanying commentary, Dr. Gilbert Welch of Dartmouth Medical School estimated that for every 2,500 women age 50 who receive a mammogram, only one will avoid dying of breast cancer, and as many as 1,000 will be told that doctors have seen something suspicious, with ~500 of these undergoing a biopsy and 5-10 undergoing unnecessary treatment.

MEDTRONIC's Infuse Bone Graft – on-label use helpful but not off-label use

The Medicare Evidence Development & Coverage Advisory Committee (MEDCAC) voted that the level of evidence was adequate to conclude that on-label use of Infuse, a bone morphogenic protein (BMP), in the lumbar spine and in open tibial fractures improved clinically meaningful health outcomes. However, the committee also voted that the evidence was not adequate to conclude that off-label use of Infuse in cervical or lumbar fusion improved clinically meaningful outcomes. Off-label use accounts for as much as 85% of use of this product.

A study published last year in the ***Journal of the American Medical Association*** found that BMP increased complications. Several panelists expressed concern about the dearth of non-industry-funded BMP studies.

The Centers for Medicare and Medicaid Services (CMS) is under no obligation to follow the MEDCAC recommendations. The panelists at the meeting did not address whether or when Medicare should pay for BMPs. CMS could revise coverage policy, allow coverage for patients who participate in a study, or allow Medicare Administrative contractors to set policy in their respective regions. If CMS decides to restrict reimbursement, it could revise its policy to reimburse only the fusion procedure but not the BMP used in the procedure. CMS also could choose to open a National Coverage

Decision, which would start a time clock to which it would have to adhere in making a final coverage decision.

MYREXIS' MPC-9528 – inhibits tumor growth

Key findings from preclinical studies with MPC-9528 were presented at the Cancer and Metabolism: Pathways to the Future Symposium held in Edinburgh, Scotland, recently. Evidence was presented demonstrating that treatment of cancer cells with MPC-9528, resulted in significant growth inhibition and that co-administration of niacin improves its therapeutic index. The researchers evaluated 145 cell lines across diverse cancer types and found ~40% of all cancers may carry the biochemical defect that makes them respond well to the combination of niacin and MPC-9528 treatment. The hope is that a simple companion diagnostic tool could be used to identify patients with susceptible tumors.

Oxygen therapy in MI patients – concerns over use in some patients

Supplemental oxygen is currently given to virtually all patients in the early phase of a myocardial infarction (MI). However, a study published in the ***Journal of the American College of Cardiology*** questions the practice and calls for prospective, large-scale randomized trials as well as revision of the current STEMI guidelines pertaining to oxygen therapy. The researchers reviewed data on the effects of supplemental oxygen in normoxic patients with acute coronary artery disease. They noted, "Excessive use of supplemental oxygen in normoxic cardiac patients could potentially lead to worse outcomes in a number of patients."

The same issues were raised in a ***Cochrane Review***, which found three times more deaths occurred among patients randomized to oxygen therapy vs. those who had been given air, and there were no benefits in terms of pain relief.

The European Society of Cardiology is expected to publish revised guidelines in 2012.

ROCHE's Avastin (bevacizumab) – European regulators reviewing use in early breast cancer

At the request of the EMA, the Committee for Medicinal Products for Human Use (CHMP) has started a review of Avastin in combination with paclitaxel or docetaxel for the first-line treatment of metastatic breast cancer in view of data from the RIBBON-1 study. Roche had requested a new indication for Avastin based on RIBBON-1. A decision is expected by the end of this year. The FDA's Oncologic Drugs Advisory Committee voted in July 2010 that Avastin should ***not*** keep its label for first-line metastatic breast cancer in the U.S., but the FDA has not yet issued a final decision.

SANOFI-AVENTIS's Plavix (clopidogrel) – study disputes PPI interaction

Controversy has surrounded the dual use of Plavix and proton pump inhibitors (PPIs), raising questions as to whether the combination affects the clinical efficacy of Plavix or might actually increase the risk of cardiovascular events. An analysis of more than 56,000 patients followed for one year after a first MI, published in the *Annals of Internal Medicine*, found that those receiving both types of drugs had the same hazard ratio for cardiovascular events as those who received only PPIs.

While dual PPI/Plavix use was not associated with any additional risk for adverse cardiovascular events over PPIs alone, PPIs alone were associated with increased risk. The researchers suggested, however, that the increased risk may not have resulted from the PPIs themselves but from differences in baseline comorbid conditions that were unmeasured or measured imperfectly.

In an accompanying editorial, Dr. Joao Paulo de Aquino Lima of Brazil and Dr. James Brophy of Canada urged that the study not be interpreted as a condemnation of PPIs in cardiovascular patients, "In assessing the risk:benefit ratio of combining clopidogrel and PPIs, it is essential to include all relevant health outcomes. Narrow interpretations of regulatory recommendations that examine only part of this clinical equation do a disservice to those seeking to optimize the overall quality of patient care."

TRANSITION THERAPEUTICS' TT-223 – development halted

Transition Therapeutics has stopped development of this gastrin analog after it failed to meet the efficacy endpoints in a Phase II trial in Type 2 diabetics. The randomized, double-blind, placebo-controlled study evaluated the safety, tolerability, and efficacy of daily TT-223 treatments, in combination with weekly administration of Lilly's proprietary GLP-1 analog for four weeks with a five-month follow-up. Dr. Tony Cruz, chairman/CEO of Transition Therapeutics, said, "While TT-223 has shown efficacy through development, these results indicate that it does not have the product profile for a diabetes therapy."

VALEANT PHARMACEUTICALS' taribavirin – alternative to ribavirin for HCV

Researchers at 51 centers in the U.S. participated in a Phase IIb randomized, open-label, active-controlled, parallel-group study involving 278 hepatitis C patients with genotype 1 who were stratified by body weight and baseline viral load. The aim of the study was to determine if weight-based dosing of taribavirin (TBV), an oral prodrug of ribavirin (RBV), demonstrated efficacy comparable to RBV, while maintaining its previously demonstrated anemia advantage with fixed dose administration.

Patients were randomized to receive TBV (20, 25, or 30 mg/kg/day) or RBV (800 to 1400 mg/day) with Roche's PegIntron (pegylated interferon alfa-2b) for 48 weeks. Weight-based dosing of TBV achieved comparable efficacy to RBV. This was observed in all three TBV weight-based dose treatment groups. Patients treated with TBV also had less than half the anemia vs. RBV-treated patients. The results suggest weight-based dosing of TBV provides a safe and effective treatment alternative to RBV for HCV. Specifically, the 25 mg/kg/day dose offered the optimal balance of efficacy and safety in this patient population.

FDA News

FDA to hold public hearing on generic biologicals

The FDA will hold a public hearing on November 2 and 3, 2010, to obtain input on the Agency's draft regulations for the approval of generic versions of biological products. The healthcare reform law recently passed by Congress allows the FDA to approve generics for biological products, following 12 years of patent exclusivity.

Topics have not yet been determined, but the focus is likely to include defining terms – e.g., "highly similar," "minor differences," and "clinically significant differences" – and clarifying the approval criteria. The FDA also may ask the panel if there are certain biologic products/classes for which bioequivalence studies should not be appropriate for approval of a biosimilar product.

Other issues that may be discussed include:

1. How to demonstrate non-inferiority on efficacy and safety.
2. Appropriate non-inferiority margins.
3. How to detect/rule out rare adverse events.
4. Acceptable immunogenicity data.
5. Whether the FDA should issue guidance documents.
6. Which products will not quality for abbreviated applications.

Drug shortages

The non-profit Institute for Safe Medication Practices (ISMP) warned recently about drug shortages that are occurring with increasing frequency, with emergency drugs, pain medications, and anesthetic agents particularly affected. The ISMP published a new survey, which reflects the responses of 1,800 practitioners, 68% of them pharmacists. The survey found 84% of respondents said that the FDA or manufacturers did not provide enough warning about drug shortages.

Respondents also were upset that the duration of shortages is rarely revealed, alternative drugs cannot be located, hoarding could become an issue, and physicians became angry at pharmacists, nurses, or hospitals when drug shortages occurred. The Institute called for a meeting with the FDA and other groups to develop a plan to reduce the occurrence of drug shortages and to better manage them when they occur.

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest

(items in red are new since last week)

Date	Topic	Committee/Event
September 2010		
September 30	Meeting on clinical trials for the development of **pediatric cardiovascular devices**	FDA public workshop
October 2010		
October TBA	**Allergan's Botox** (onabotulinumtoxinA) for chronic migraine	PDUFA date
October 4	**FDA 510(k) reform comments**	Deadline for public comments
October 8	Clinical trial design recommendations for **devices for the treatment of depression**	FDA's Neurological Devices Advisory Committee
October 12	**Alkermes' Vivitrol** (naltrexone ER injection) for opioid dependence	PDUFA date
October 18	**Amgen's Aranesp** (darbepoetin) for anemia in chronic kidney failure	FDA's Cardiovascular and Renal Drugs Advisory Committee
October 19	**Boehringer Ingelheim's Pradaxa** (dabigatran), an anticoagulant	PDUFA date
October 22	**Arena Pharmaceuticals/Eisai's lorcaserin**, a diet drug	PDUFA date
October 22	**Lilly/Amylin's Bydureon** (exenatide long-acting) for Type 2 diabetes	PDUFA date
October 24	**Warner Chilcott's Actonel delayed-release** (risedronate) for osteoporosis	PDUFA date
October 28	**Vivus's Qnexa** (phentermine + topiramate), a diet drug	PDUFA date
November 2010		
November 2-3	Draft of regulations for **generic biologics**	FDA public hearing
November 16	**GSK/Human Genome Sciences' Benlysta** (belimumab) for lupus	FDA's Arthritis Advisory Committee
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	**GlaxoSmithKline/Valeant's ezogabine** for epilepsy	PDUFA date
December 2010		
December 2	**Oceana Therapeutics' Solesta** for fecal incontinence	FDA's Gastroenterology and Urology Devices Advisory Committee
December 3	**Allergan's Lap-Band Adjustable Gastric Banding System**	FDA's Gastroenterology and Urology Device Advisory Committee
December 7	**Orexigen Therapeutics' Contrave** (naltrexone + bupropion), a diet drug	FDA's Endocrinologic and Metabolic Drugs Advisory Committee
December 7	**AstraZeneca's Brilinta** (ticagrelor), an anticoagulant	New PDUFA date
December 7	**Salix Pharmaceuticals' Xifaxan** (rifaximin) for non-constipation IBS	PDUFA date
December 9	**GSK/Human Genome Sciences' Benlysta** (belimumab) for lupus	PDUFA date
December 17	**AstraZeneca's Brilinta** (ticagrelor), an anticoagulant	Revised PDUFA date
December 25	**Bristol-Myers Squibb's ipilimumab** for advanced melanoma	PDUFA date
Other future meetings		
January 7, 2011	**Endo Pharmaceuticals' tamper-resistant Opana ER** (oxymorphone), a pain killer	PDUFA date
January 31, 2011	**Orexigen Therapeutics' Contrave** (naltrexone + bupropion), a diet drug	PDUFA date
Date TBA, 2011	Review of **accelerated drug approval process**	FDA's Oncologic Drug Products Advisory Committee (ODAC)
Summer 2011	Report on **FDA 510(k) reform**	Institute of Medicine