TRENDS-in-MEDICINE

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Quick Takes

…Highlights from this week's news relating to drugs and devices in development that are not covered in other *Trends-in-Medicine* reports…

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SHORT TAKES

- **ADVANCED BIONICS' HiRes 90K** cochlear implant received a CE Mark after making changes to its manufacturing process.
- **AMIRA PHARMACEUTICALS' AM-152** for idiopathic pulmonary fibrosis was granted orphan drug status by the FDA.
- **AMYLIN and LILLY and ALKERMES' Bydureon (exenatide once-weekly) –** The European Medicines Agency (EMA) said this once-weekly injectable drug is suitable for adults with Type 2 diabetes. The FDA rejected Bydureon last year, saying it needed further study. *This is another example of where the FDA and EMA don't see eye-to-eye.*
- **ANULEX TECHNOLOGIES** laid off workers after it received an FDA warning letter in February 2011 saying it failed to file an investigational device exemption application before conducting a postmarket study of its Xclose device, which is used for soft tissue repair.
- **AVITA MEDICAL's ReCell Spray-On Skin –** A small pilot study of four patients suffering from deep dermal flame burns showed the patients healed quickly when treated with the spray-on skin combined with a biological dressing.
- **BAXTER INTERNATIONAL** is buying **Prism Pharmaceuticals**, which makes the arrhythmia drug Nexterone (amiodarone).
- **BECKMAN COULTER's troponin test –** The company delayed two FDA submissions for its troponin test until 3Q11 to work on quality and compliance initiatives.
- **Breast implants –** A report in ***Plastic and Reconstructive Surgery*** said there is a *definite* link between breast implants and development of a rare type of lymphoma, anaplastic large cell lymphoma (ALCL), which typically involves a seroma in the fibrous capsule around a breast implant. An expert panel concluded ALCL is probably under-identified and under-reported.
- **BRIDGEPOINT's CrossBoss and Stingray CTO catheters** as well as the Stingray guidewires were found to be safe and effective for intra-luminal placement beyond coronary CTOs when compared to conventional devices in a multicenter trial.
- **CHELSEA THERAPEUTICS' Northera –** Chelsea plans to file a new drug application (NDA) in 3Q11 for this orphan drug for Parkinson's disease.
- **CUMBERLAND PHARMACEUTICALS' Hepatoren (ifetroban) –** Cumberland acquired the rights to the ifetroban molecule from Vanderbilt University and will test it

as a potential in-hospital treatment for a condition involving progressive kidney failure. The company plans to develop the molecule as an orphan drug.

- **Drug discovery** – A University of Missouri professor figured out how highly pressurized carbon dioxide can bring about crystallization of drug compounds in a fraction of the time compared to the current method.

- **FUTURA MEDICAL's CSD500** – a condom with a gel that helps men maintain a firmer erection for a longer period of time – reportedly is close to receiving regulatory approval in Europe, perhaps by the end of 2011.

- **Generic drugs** comprised 78% of all prescriptions dispensed last year, according to an IMS Institute for Healthcare Informatics study. The top prescribed drug was hydrocodone/acetaminophen.

- **Genetic testing** – Parents generally believe the benefits of pediatric genetic testing outweigh the risks, according to a study of more than 200 parents published in ***Pediatrics***.

- **GILEAD SCIENCES' Truvada (emtricitabine + tenofovir disoproxil fumarate)** – The FEM-PrEP trial of Truvada for preventing HIV infection in at-risk women was stopped due to lack of efficacy. An equal number of women taking Truvada became infected with HIV as those not taking it.

- **GLAXOSMITHKLINE's Pandemrix** – While a comprehensive review on a possible link between the flu vaccine and narcolepsy in children is not due to be completed until July, the EMA ordered a label change instructing doctors to weigh a potential narcolepsy risk when considering this H1N1 vaccine in children and teens.

- **Hemodialysis mortality** – Data from an observational study published in the ***Journal of the American Society of Nephrology*** found that patients undergoing hemodialysis (HD) using a central catheter placed into one of the large veins may be at a higher risk of early death than patients on peritoneal dialysis (PD). During the first year, the risk of death was 80% higher for HD than PD.

- **Hip replacements** – Shortened hospital stays after hip replacement surgery may lead to extended rehabilitation time in skilled nursing facilities and to increased rates of rehospitalization due to complications, according to University of Iowa researchers writing in the ***Journal of the American Medical Association***.

- **HIV drugs** – A European study showed that ~10% of HIV-positive children (a cohort in the PLATO-II trial) were resistant to medications in all three of the original antiretroviral drug classes. The cumulative risk for triple-class virological failure after five years of medications was 12%.

- **IMQUEST BIOSCIENCES' IQP-0528** – This anti-HIV vaginal gel showed promise in mouse models. Human trials are planned in 2012 for a vaginal microbiocide gel/drug formulation.

- **INFRAREDX's LipiScan IVUS coronary imaging system** received a CE Mark, making it the only IVUS approved in Europe and the U.S.

- **Kidney injury marker** – Neutrophil gelatinase-associated lipocalin (NGAL), a biomarker in urine or blood, detected early subclinical acute kidney injury (AKI) and its adverse outcomes in critically ill patients who did not have diagnostic increases in serum creatinine, according to a study published in the ***Journal of the American College of Cardiology***.

- **LILLY/ALNARA PHARMACEUTICALS' Sollpura (liprotamase)**, a pancreatic enzyme replacement therapy, was rejected by the FDA, which said another clinical trial is needed before the drug can be resubmitted. In January 2011, the FDA's Gastrointestinal Drugs Advisory Committee voted 7 to 4 (with one abstention) that the risk:benefit did ***not*** favor approval of this pancreatic enzyme replacement therapy. Safety wasn't really the issue; the panel just wasn't convinced of the efficacy.

- **NICOX's naproxcinod** – NicOx withdrew its CE Mark application for this anti-inflammatory drug. The FDA rejected the drug last year.

- **NIH budget** – The final budget agreement approved by the Senate and House cuts $260 million, or 0.8%, from the National Institutes of Health (NIH) budget vs. 2010.

- **NOVARTIS's Prexige (lumiracoxib)** – The EMA said Novartis withdrew its application to reintroduce this pain reliever for osteoarthritis.

- **REGENERON's aflibercept (VEGF Trap-Eye)** – The FDA gave priority review status to this treatment for age-related macular degeneration (AMD).

- **STERIS CORPORATION's System 1 processor** – The FDA extended the deadline to February 2, 2012, for companies to switch from Steris Corporation's System 1 processor (SS1) to legal alternatives.

- **THREE RIVERS PHARMACEUTICALS' Infergen (interferon alfacon-1)** – The FDA sent a warning letter to Samuel Waksal, PhD, of **Kadmon Pharmaceuticals**, saying a STATgram for the Infergen injection for subcutaneous use

by Three Rivers, a Kadmon company, was false or misleading.

- **Triglycerides** – The American Heart Association said in a statement in ***Circulation*** that the use of medications to lower triglycerides "is still lacking crucial clinical trial evidence" and diet and lifestyle changes alone can reduce triglycerides.
- **ViroPharma's Vancocin** – A federal court rejected the company's motion to overturn an FDA advisory committee's recommendation that drug manufacturers that want to market generic Vancocin do not have to perform clinical trials in humans.
- **XTL Biopharmaceuticals' recombinant erythropoietin** – The company applied to the FDA for orphan drug status for this drug, which is in Phase II development, to treat multiple myeloma.

News in Brief

Allergan's Botox (onabotulinumtoxinA) – mutes emotional response

A study published in the journal ***Social Psychology and Personality Science*** found that in addition to removing wrinkles Botox may remove (or lessen) a person's ability to understand the emotions of others. Researchers at the University of Southern California and Duke University conducted two experiments:

- A 31-patient study of Botox vs. **Medicis**'s Restylane, a dermal filler.
- A 95-patient study of Botox vs. a gel that amplifies muscular signals.

The participants in both experiments viewed computer images of faces and identified the emotions they saw. They found that when the facial muscles were dampened (with Botox), the person had worse emotion perception, and when the facial muscles were amplified (with the gel), they were better at emotion perception.

Argus' Argus II Retinal Prosthesis System – gets European approval

The first retinal prosthesis, an implantable device for profoundly blind people with degenerative diseases including retinitis pigmentosa, received a CE Mark. The system converts video taken by a miniature camera set in a patient's eyeglasses into electrical pulses, which are then transmitted wirelessly to a 60-electrode grid attached to the retina. The pulses stimulate the retina's remaining cells and patients learn to interpret visual patterns.

AstraZeneca/Millennium and Johnson & Johnson's Velcade (bortezomib) – SQ as good as IV but fewer adverse

A subcutaneous (SQ) formulation of Velcade helped relapsed multiple myeloma patients live just as long as patients treated with the conventional IV formulation, but SQ patients had fewer adverse events, according to a study published in ***The Lancet Oncology***. One-year survival did not differ between SQ and IV Velcade, meeting the primary endpoint of non-inferiority, but the median time to progression (TTP) was longer with SQ (10.4 months vs. 9.4). In addition, hematologic and non-hematologic toxicities, especially peripheral neuropathy, occurred less often with SQ.

Bayer

- **Xarelto (rivaroxaban)** was submitted to the Japanese Ministry of Health, Labor, and Welfare. This oral anticoagulant is indicated for the prevention of stroke in atrial fibrillation patients.
- **Yaz, Yasmin (drospirenone/ethinyl estradiol)** – A large retrospective cohort study of nearly 3 million women using this birth control method, which combines ethinyl estradiol with one of seven progestins, found a small but statistically significant increase in the risk of having gallstones or gallbladder disease.

Biogen Idec and Elan's Tysabri (natalizumab) – new label warnings

First, the EMA rewrote this multiple sclerosis drug's label to include a reference to JC virus antibody status as a risk factor for progressive multifocal leukoencephalopathy (PML).

Then, the FDA updated the label with new information about the risk of PML, but did not mention JCV status. However, the FDA did say it still believes the benefits of taking Tysabri outweigh the potential risks.

The revised FDA label includes:

- A table summarizing rates of PML with Tysabri use. The FDA said 102 cases of PML have been reported among 82,732 patients treated with Tysabri worldwide through February 28, 2011. The FDA also acknowledged that the PML risk increases with the duration of therapy, with the risk greater in patients who have received >24 Tysabri

infusions (corresponding to two years of continuous treatment) vs. those who received <24 infusions.

Previously, the FDA showed cumulative risks above certain thresholds of exposure, but the Agency is now reporting it for specific periods, explaining that this should "allow prescribers to better assess risk based on duration of treatment and will aid healthcare professionals in discussing the risk of PML with their patients." The FDA added that the PML rates in the U.S. and the rest of the world have become "more similar," so it is not giving the PML risk by geographic location.

PML Risk with Tysabri	
Duration of therapy (number of infusions)	**PML incidence per 1,000 patients**
≤24 months	0.3
25-36 months	1.5
37-48 months	0.9

*Data as of January 2011, and data beyond 4 years of treatment are limited.

- Information on a "newly identified" PML risk factor: ***prior*** use of an immune suppression medication (e.g., azathioprine, cyclophosphamide, mitoxantrone, methotrexate, mycophenolate). The label already warned against concomitant use but not prior use.

Brain chemical pathway – may explain some stress-associated disorders

A report in ***Nature*** said a previously unknown chemical pathway in the brain may explain why some people are more susceptible to stress-associated psychiatric disorders, including depression, anxiety, and post-traumatic stress disorder. U.K. researchers found in mouse studies that stress causes the brain's emotional center, or amygdala, to increase neuropsin production, which triggers a series of chemical events causing the amygdala to increase its activity. That activity switches on the Fkbp5 gene, which determines the stress response at a cellular level. *Expect some drug discovery to be directed at this.*

ELI LILLY's Effient (prasugrel) – reduces platelet reactivity better than Plavix

Patients taking Effient had significantly lower levels of platelet reactivity after percutaneous coronary intervention (PCI) vs. those on **Sanofi-Aventis**'s Plavix (clopidogrel), according to a report in the ***Journal of the American College of Cardiology Cardiovascular Interventions***. Greek researchers said high on-treatment platelet reactivity occurred in five times as many patients taking Plavix as Effient. The effect was better in patients carrying one CYP2C19*2 allele.

GLAUKOS' iStent – positive results

Implantation of this trabecular micro-bypass stent in junction with cataract surgery was more effective at reducing IOP and lowering the use of medication than cataract surgery alone, according to a 240-eye, prospective, randomized controlled study published in ***Ophthalmology***. At one year postop, an unmedicated IOP of ≤21 mmHg was achieved by 72% of iStent eyes vs. 50% of control eyes, and ≥20% IOP reduction without medication was achieved by 66% of iStent eyes vs. 48% of control eyes (p=0.003).

HEARTWARE's HVAD device – thrombus events doubled in CAP cohort

The rate of device changes due to thrombus increased from 2.1% to 4.4%, in the 100-patient bridge-to-transplant (BTT) trial in the continuous access protocol (CAP) cohort, indicating that thrombus events increase over time with this left ventricular assist device. Reportedly, HVAD patients now have a 9.2% chance per year of developing a blood clot. The company said this could slow down enrollment in its destination therapy (DT) trial. In other news, the FDA said HeartWare can implement a surface finish modification (sintering) to its device for both DT and CAP patients. HVAD already is approved in Europe.

JOHNSON & JOHNSON

- **Duragesic (fentanyl transdermal)** – The FDA said "manufacturing issues" are causing a shortage of this topical painkiller.
- Is in talks to buy **Synthes**, which would make J&J the clear leader in the trauma market, add to its spine segment, and enhance its position in the overall orthopedic market.
- **CoStar** – Eight-month results from the EUROSTAR-II study showed this paclitaxel-eluting stent is as safe and effective as a bare metal stent, with lower rates of restenosis, revascularization, and late lumen loss in patients with *de novo* coronary artery stenosis.

NEURALSTEM's stem cell therapy – safe in ALS patients

Stem cell therapy is safe for people with amyotrophic lateral sclerosis (ALS), according to interim data presented at the American Academy of Neurology meeting in Hawaii. Researchers said the first nine patients receiving the therapy are still alive 4-15 months after surgery. The Phase I study will continue with 18 patients.

NOVARTIS's Ilaris (canakinumab) – positive results in gout

This monoclonal antibody already is FDA-approved to treat rheumatoid arthritis, and data now look good as a treatment for gout. At the British Society for Rheumatology meeting, Swiss researchers reported on a 1-month trial in 200 gout patients that showed high-dose Ilaris (150 mg) was significantly better than steroids in achieving ≥75% reduction in pain by 72 hours, and 96% had ≥50% reduction in pain.

Ilaris Results in Gout

Measurement at 72 hours	Ilaris 150 mg	Triamcinolone acetonide 40 mg	p-value
≥75% reduction in pain	75%	45%	<0.001
≥50% reduction in pain	96%	61%	---
Time to 50% reduction in pain	One day	Two days	0.0006
Erythema resolved by Day 3	74.1%	69.6%	---
Erythema resolved by Day 7	96.3%	83.9%	---
Used rescue medications	22%	55%	0.01
Adverse events	41%	42%	---

NOVO NORDISK's NovoSeven (recombinant factor VIIa) – off-label use may be harmful

Off-label use of rFVIIa to stop heavy bleeding in patients may raise the risk for thromboembolism, according to a meta-analysis published in ***Annals of Internal Medicine***. Stanford University researchers reviewed studies of off-label use of rFVIIa, which is approved for a limited group of patients with hemophilia, and found no survival benefit from administering it to patients with intracranial hemorrhage, trauma, or cardiac surgery. They also found a slightly increased risk of thrombo-embolism in patients with intracranial hemorrhage or patients undergoing cardiac surgery.

Opioid abuse – new government initiative

The Obama administration announced a new, multi-pronged federal program to curb abuse of long-acting (LA) and extended-release (ER) prescription opioids – the Prescription Drug Abuse Action Plan. Under the plan the pharmaceutical industry will educate providers and patients about the appropriate use and handling of opioids through FDA-approved programs and materials, and the Drug Enforcement Administration (DEA) will ensure doctors get the training by making it a condition of their DEA license to prescribe controlled substances. Currently, DEA doesn't have the authority to link training to licensure, but the administration plans to ask Congress to change the law and give DEA that authority.

This effort is a collaboration by four agencies: DEA, FDA, the White House Office of National Drug Control Policy (ONDCP), and the U.S. Department of Health and Human Services (HHS).

The key elements of the plan are:

- Expansion of state-based prescription drug monitoring programs. These are already in place in many states, but other states, such as Florida, have rejected the idea so far. And even where they are in place, only a relatively low percentage of doctors participate.
- Recommending convenient and environmentally responsible ways to dispose of unused opioids.
- Education for patients and healthcare providers on safe and appropriate use of these drugs.
- Reducing the number of "pill mills" and doctor-shopping through law enforcement.

FDA is implementing a Risk Evaluation and Mitigation Strategy (REMS) for all ER and LA opioid medications by 16 brand and generic manufacturers. The new REMS plan is basically an education plan that focuses on educating doctors about proper pain management and patient selection and educating patients on how to use, safeguard, and dispose of these drugs safely.

FDA officials explained their efforts in a teleconference with reporters.

Pharmas have 120 days to work together and develop a ***single system*** for implementing the REMS. That is, the FDA sent a letter to the pharmas telling them they ***must*** propose a REMS plan within 120 days. Once the pharmas submit their REMS, the FDA will review the educational materials developed to make sure they are not promotional and that they conform to the Agency's intent, which is to "convey the information in an unbiased manner." Some back-and-forth is expected, but the FDA hopes to have a final REMS by early 2012.

This is a physician/patient program. Pharmacists are ***not*** involved, and there are no new requirements for pharmacists.

That new REMS must:

- **Educate doctors** on how to select patients, how to spot abusers/misusers, how to initiate therapy, and the risks and adverse events.
- Help doctors **counsel patients** on use, safe storage, and disposal of opioids. Doctors, not pharmacists, will do the counseling.
- Include **provider/patient agreements**. And the FDA would like a standardized agreement.

- Include a new MedGuide. Janet Woodcock, MD, director of the FDA's Center for Drug Evaluation and Research (CDER), said this will be a "more standardized and comprehensive leaflet…on how to take [the drugs], symptoms of overdose, concomitant use of other depressants or alcohol, the risk associated with sharing, how you might discontinue taking it, proper storage in the household, and proper disposal…It is fairly extensive, but we will try to boil it down, so we don't overwhelm them but see that they have the information they need."
- Have a way to **monitor the program** and to measure the program's efficacy, both in terms of preventing abuse and misuse and in ensuring patient access to needed medications. Pharmas will be required to show that they trained a prespecified number of providers.
- The pharmas will be expected to provide the **material to the continuing medical education (CME) providers** – and the FDA has already discussed that expectation with several CME companies – who will then be expected to offer the training to clinicians. There will also be an independent audit of the materials used by the CME providers to be sure they are unbiased and effective, including testing to see how well the people being trained are comprehending the material.

Dr. Woodcock called this effort the "most far-reaching REMS the FDA has instituted…It is our intention and hope that through the tools provided by the opioid REMS…prescribers will feel more knowledgeable and comfortable in prescribing these drugs and better able to identify patients who should be referred for treatment or should not be getting these medications."

She said it is just the first step in a step-wise approach to ensure prescribers get information on appropriate pain management and use, adding, "If, in fact, we find that this first step is not effective, there are additional steps that can be taken." However she did not elaborate as to what additional steps the FDA could or might take.

Dr. Woodcock said linking opioid education to a doctor's DEA registration is "the most efficient way to accomplish and ensure providers are trained because it would not require another system to verify providers are trained…If this legislation does not happen, we can evaluate at the FDA other means of accomplishing that, but currently this is the path we want to pursue."

Asked if the new REMS will affect the transmucosal fentanyls (e.g., Meda's Onsolis and Cephalon's Actiq and Fentora), Dr. Woodcock said no, "Those products are fairly high risk and have their own REMS. We are not planning to fold that into this because of the level of risk. This applies to the long-acting oral fentanyl, not the transmucosal or immediate-release fentanyl."

Asked if the FDA supported the DEA linkage to licensing, Dr. Woodcock said, "Oh, yes, we and HHS all support this…A lot of new opioids have been introduced, and many prescribers will never have been trained on the characteristics of those. When I went to medical school, we didn't have the extended-release opioids…and as newer medications come on, it is critical that all people who will write for controlled substances be trained in this."

What happens if Congress doesn't change the law and give DEA this authority? Dr. Woodcock said, "If the legislation is not enacted or the training fails to meet the target in terms of the number of physicians trained, then we will contemplate other actions …By doing this through continuing education, we do put some incentives in because providers are required to complete a certain number of hours of continuing medical education."

Asked how pharmas will know if abuse is being curtailed, Gerald Dal Pan, MD, director of the FDA's Office of Surveillance and Epidemiology, CDER, said, "Our epidemiologists here have looked at a wide variety of data sources…There is no one specific data source that will answer all our questions…We take data from different sources and piece it together… Companies may be interested in using these data sources or developing data sources of their own."

It is likely that the FDA and the administration will expect to see a decrease from the figures they cited in announcing this initiative, which were:

- >50% of opioid abusers get their drugs from a friend or relative, according to a 2007 survey.
- >33 million Americans age ≥12 misused extended-release and long-acting opioids in 2007, up from 29 million in 2002.
- Nearly 50,000 emergency room visits were related to opioids in 2006.
- More people unintentionally overdosed on prescription drugs than overdosed during the crack cocaine epidemic of the 1980s and the black tar heroin epidemic of the 1970s.
- Nearly 12,000 Americans died from opioid overdoses in 2007.

PFIZER's tofacitinib (previously tasocitinib) – safety issues with 10 mg BID and efficacy questions with 5 mg BID

The release of the late breaker abstract (LBA005 on the ORAL-SYNC trial) from the EULAR (European League

Against Rheumatism) conference in June 2011 on tofacitinib raised questions about the safety of this oral rheumatoid arthritis (RA) medication.

It appears that Pfizer may have been less than forthcoming about the safety of tofacitinib. When the company released the initial topline data from ORAL-SYNC, it said there were no new safety signals or issues. Perhaps it would have been more prudent for Pfizer to say that there were unrelated deaths, etc.

Questions about the safety of tofacitinib first arose when the Phase II data were presented at the American College of Rheumatology (ACR) meeting in November 2010. There was a drop in hemoglobin as well as increases in ALT, AST, and creatinine that didn't resolve on treatment over two years. And there were questions about whether or how well they resolve when treatment is discontinued.

The issues with the EULAR data appear to be:

1. **Deaths.** There were four deaths in ORAL-SYNC. There was 1 death in the ORAL-SOLO, which was presented at ACR – a 79-year-old Bulgarian at 10 mg with a history of cardiovascular (CV) disease and diabetes who developed diarrhea followed by renal failure, hyperkalemia, and fatal asystole. So, the 4 ORAL-SYNC deaths are not the first deaths in the tofacitinib Phase III trials, and there are now a total of 5 deaths (though, remember that these are crossover trials). Obviously, the traumatic brain injury death is not a concern, but:
   a. The rheumatoid arthritis death (at 5 mg BID, 42 days after discontinuation) *could* be CV-related since inflammation of the pericardium is an issue in RA and since CV mortality is significantly higher in RA than in the general population. Pfizer says it is not drug related.
   b. The respiratory failure (at 5 mg BID) seemed unrelated, but in looking over the ORAL-SOLO data, it makes this death look less isolated. There was pleurisy, pneumonia, and pulmonary fibrosis with the 10 mg BID dose, COPD at both doses (1 case at 5 mg and 2 cases at 10 mg) as well as serious pleural effusion in ORAL-SOLO. So, there *could* be some lung issue going on for which we have not yet seen a mechanistic explanation. Pfizer claims this death is the only one of the four in ORAL-SYNC that is drug-related.
   c. One case of acute heart failure (at 10 mg BID) that Pfizer says the investigator deemed not related to the drug. However, there were three cases of CHF in ORAL-SOLO.
2. **Opportunistic infections.** These are less concerning because that is also a problem with the TNF inhibitors. While the infections with TNF inhibitors made the FDA crazy in the early days of those biologics, everyone – doctors, patients, and the FDA – seem to have gotten comfortable with them. Nothing with tofacitinib looks remarkably different from the TNF experience in terms of opportunistic infections, except the rate appears lower. The rate was 1.2% in ORAL-SOLO, and there are 4 out of ~400 patients in ORAL-SYNC, so it is about the same range.

On top of this, the six-month results of the Phase III ORAL-SCAN trial had mixed results in moderate-to-severe RA patients with inadequate response to MTX. The 10 mg BID dose met all the primary endpoints vs. placebo, significantly reducing the signs and symptoms of RA and reducing the progression of structural joint damage at six months, and improving physical function at three months. Patients on tofacitinib also showed greater remission at six months. However, the 5 mg BID dose did not significantly reduce the progression of structural joint damage. Results of two more Phase II studies will be released in mid 2011.

Bottom line: The FDA review of this drug could get ugly and is likely to involve a deep dive into the data. The FDA probably will take a long, hard look at the CV risk. With the radiographic efficacy of the 5 mg in question and the safety of the 10 mg raising questions, this could be a tricky balance for the FDA. It wouldn't be a surprise if the FDA required a CV outcomes trial, but probably post-approval.

The tofacitinib program includes:

- **ORAL-SOLO** (1045 trial) was presented at ACR 2010 (monotherapy in DMARD failures – which could include biologic failures). This is a 6-month trial, which had 3 cases of congestive heart failure and 1 death.
- **ORAL-SYNC** (1046 trial). Topline results were reported March 4, 2011. Patients were ≥1 DMARD failures (non-biologic) studied for 12 months. There were 4 deaths (one clearly was not drug-related, and the others remain to be adjudicated by the FDA).
- **ORAL-SCAN** (1044 trial). This is the radiographic trial of tofacitinib + methotrexate (MTX) vs. MTX. Six-month topline results were reported, but the trial runs for 24 months (to February 2012). The 10 mg BID dose showed statistically significant results on radiographic progression at six months, but the 5 mg BID dose did not, but the exact numbers are not known. Additional updates are expected at 12 months, maybe 18 months, and certainly at 24 months.
- **ORAL-1064** (1064 trial). This is a trial of tofacitinib head-to-head vs. Abbott's Humira (adalimumab) vs. placebo in MTX-incomplete responders. The primary endpoints are

ACR20 and HAQ at 6 months. It was due to complete in March 2011, so there may be topline results in the next few months and maybe a late-breaker at ACR.

- **ORAL-1032** (1032 trial). This is a six-month trial of tofacitinib + MTX vs. placebo + MTX in TNF-inadequate responders. The primary endpoints are ACR20, DAS28, and HAQ-DI. This also was due to finish in March 2011, so there may be topline results in the next few months and maybe a late-breaker at ACR.
- **ORAL-1069** (1069 trial). This is a 24-month trial of tofacitinib vs. MTX in MTX-naïve patients. The primary endpoint is hand & foot radiographs (for EMA registration) and ACR70. This is due to finish in May 2013.
- **The 1024 trial.** This is an open-label, long-term efficacy and safety study. It is enrolling patients who complete the Phase II and III trials, with plans to enroll 4,000 patients and follow them for "several years." This trial is expected to complete in January 2015.

PFIZER and MEDIVATION's Dimebon (latrepirdine) – fails in Huntington's disease

Dimebon failed to show efficacy in the HORIZON Phase III trial in patients for cognition and global improvement. Phase II data from an earlier Russian trial showed the drug not only slowed progression of Alzheimer's disease but reversed cognitive decline. The Phase III CONCERT trial of Dimebon in Alzheimer's disease patients will continue as planned with results expected in early 2012.

Statins and anti-hypertensives – not cost-effective

A Finnish study published in the ***British Medical Journal*** (BMJ) said there is no evidence statins or anti-hypertensives used to reduce risk of cardiovascular events are cost-effective. The researchers argued for large-scale studies to look at the cost-effectiveness of certain treatments and criticized some cost-savings models.

TAKEDA's Actos (pioglitazone) – new bladder cancer risk data

Data from a study published in the journal ***Diabetes Care*** shows that using Actos for more than two years may increase a patient's risk for bladder cancer. Researchers studying the Kaiser Permanente Northern California Diabetes registry of 30,173 Type 2 diabetics-patients showed patients on Actos for more than two years had a significant 1.4-fold increased risk for developing bladder cancer vs. non-users.

REGULATORY NEWS

CMS proposed decision on ESAs criticized

Public Citizen wrote a letter to the Centers for Medicare and Medicaid Services (CMS) opposing the proposed decision memo on using erythropoiesis-stimulating agents (ESAs) to treat adults with chronic kidney disease (on dialysis and not on dialysis). Public Citizen said the use of ESAs contains unknown risks and benefits, doesn't align with the FDA's black box warning on the drugs, and contributes to wasteful spending of Medicare dollars.

FDA changing hemorrhoid prevention pressure wedge to Class II (special controls)

The FDA said it is reclassifying the hemorrhoid prevention pressure wedge into Class II to provide a reasonable assurance of safety and effectiveness of the device. The wedge provides support to the perianal region during labor and delivery.

FDA requiring postmarketing tests for asthma drugs

The FDA is requiring postmarketing studies to look at the safety of long-acting beta-agonists (LABAs) when combined with inhaled corticosteroids for patients with asthma. Four trials are expected to begin this year and will enroll 46,800 patients. The FDA is also asking **GlaxoSmithKline** to separately evaluate its Advair Diskus (fluticasone propionate) in 6,200 children aged 4 to 11.

FDA revises guidance for devices

The FDA issued revised guidance explaining the types of manufacturing-related changes to approved devices that would require companies to submit a 30-day notice.

FDA strategic priorities

The FDA released the final version of its strategic priorities through 2015. These include:

- Modernizing regulatory science to draw on innovations in science and technology to ensure the safety and effectiveness of medical products throughout their life cycles.
- An integrated global food safety system focused on prevention and improved nutrition.
- Expanded efforts to meet the needs of special populations.

HHS aims to reduce hospital admissions, conditions

The Department of Health and Human Services (HHS) unveiled a new initiative to reduce hospital-acquired conditions and hospital admissions, aimed at cutting preventable injuries and illnesses in hospitals by 40% over the next three years. The plan aims to reduce preventable hospital readmissions by 20%.

Medicare plans pay cuts for hospitals

CMS released a proposed rule that would slash payments to hospitals by nearly $500 million in 2012. Under the proposed Inpatient Prospective Payment System (IPPS) rule, 3,400 acute care hospitals would see their reimbursement rates for inpatient stays cut by 0.5% in 2012.

Recent FDA approvals

- **MEDTRONIC's Valiant**, a thoracic skin graft for the repair of fusiform aneurysms or saccular aneurysms/penetrating ulcers of the aorta.
- **ROCHE's Cobas HPV test** – to identify women with the two highest-risk HPV genotypes as well as 12 other high-risk genotypes.
- **ST. JUDE MEDICAL's Trifecta**, a surgical aortic replacement valve.

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
	April 2011	
April 27	**Merck's Victrelis** (boceprevir) for HCV	FDA's Antiviral Advisory Committee
April 27	**Medicis Aesthetics' Restylane** – expanded indication for augmentation of the lips	FDA's General and Plastic Surgery Devices Advisory Committee
April 28	**Vertex Pharmaceuticals' telaprevir** for HCV	FDA's Antiviral Advisory Committee
	May 2011	
May 1	CATT trial results comparing **Roche/Genentech's Lucentis** (ranibizumab) and **Avastin** (bevacizumab) in AMD	Association for Research in Vision and Ophthalmology (ARVO)
May 2	**Safety of ultrasound contrast agents**, including new data and status of required postmarketing trials: Lantheus Medical Imaging's perflutren lipid microsphere injectable suspension (NDA); GE Healthcare's perflutren protein-type A microspheres injectable suspension (NDA); and Bracco Diagnostics' sulfur hexafluoride microbubble injection (IND)	FDA's Cardiovascular and Renal Drugs Advisory Committee meeting jointly with the FDA's Drug Safety and Risk Management Advisory Committee
May 4-5	**Biosimilar challenges and opportunities**	Joint DIA and FDLI conference
May 12	**BioMimetic Therapeutics' Augment Bone Graft**, an alternative to autologous bone grafts (PMA application)	FDA's Orthopaedic and Rehabilitation Devices Advisory Committee
May 23	**Vertex Pharmaceuticals' telaprevir**, a treatment for hepatitis C	PDUFA date
May 29	**Roche/Genentech's Lucentis** (ranibizumab) – results of Phase III trial	EURETINA Congress in London
May 30	**Optimer Pharmaceuticals' fidaxomicin** for the treatment of *C. diff*	PDUFA date
	June 2011	
June 2-3	Approaches and endpoints for devices for **seizure detection, cognitive evaluation, and traumatic brain injury/concussion assessment**	Joint workshop of the FDA, the American Academy of Neurology, the American Epilepsy Society, and the National Academy of Neuropsychology
June 17	**Celgene's Istodax** (romidepsin) – sDNA for peripheral T-cell lymphoma	PDUFA date
June 17	**Pfizer/King Pharmaceuticals' Acurox** (immediate-release oxycodone), a painkiller	PDUFA date
June 23	**Pfizer/King Pharmaceuticals/Pain Therapeutics' Remoxy** (tamper-resistant oxycodone CR) for pain	PDUFA date
June 23-24	**HCV drug development**	Workshop on Clinical Pharmacology of Hepatitis Therapy, Boston
June 28-29	**Roche/Genentech's Avastin** (bevacizumab), hearing on appeal of FDA's decision to withdraw the indication for metastatic breast cancer	FDA's Oncologic Drugs Advisory Committee (ODAC)
June 29	**Cellular and gene therapy products** for retinal disorders	FDA's Cellular Tissue and Gene Therapies Advisory Committee
	Other 2011 meetings/events	
July	**Novartis's Arcapta Neohaler** (indacaterol) long-acting beta agonist (LABA) for COPD	PDUFA date
July 20	**AstraZeneca's Brilinta** (ticagrelor), an anticoagulant	PDUFA date
August 25	**Shire's Firazyr** (icatibant) for hereditary angioedema	PDUFA date
2H11	**Abbott's RX Acculink** carotid stent	FDA final decision expected
Summer	Report on **FDA 510(k) reform**	Institute of Medicine
4Q11	**Ophthotech's ARC-1905** primary endpoint results in Phase I trial in dry AMD	Company announcement or medical conference presentation
4Q11	**Roche/Genentech's Lucentis** (ranibizumab) – Phase III HARBOR trial one-year data on the 2 mg dose in wet AMD	Company announcement or medical conference presentation
October 20	**Johnson & Johnson's abiraterone** for metastatic prostate cancer	PDUFA date
December	**Allergan's brimonidine tartrate intravitreal implant** – Phase II trial in dry AMD to complete	Company announcement or medical conference presentation
December 8	**Antares Pharma's Anturol Gel (oxybutinin gel)**, a treatment for overactive bladder.	PDUFA date
	2012 meetings/events	
February 2012	**Alcon's tandospirone** for dry AMD – Phase III final data expected	Company announcement or medical conference presentation