

# DICKINSON'S FDA Update

A WEEKLY FAX SUPPLEMENT TO DICKINSON'S FDA REVIEW

Published as a supplement of Dickinson's FDA Review by Ferdic, Inc., P. O. Box 846, Harrisburg, PA 17108-0846.  
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Annual Subscription: US\$745 - Domestic \* US\$795 - Overseas \* ©2007 Ferdic, Inc. All rights reserved.

## » Senate confirms Hamburg

The Senate 5/18 voted to confirm **Margaret Hamburg** as FDA commissioner. During a 5/7 Senate Health, Education, Labor and Pensions hearing, the 54-year-old public health physician and bioterrorism expert outlined her top five priorities if confirmed: **1.** To review FDA's work on the H1N1 influenza outbreak, **2.** To focus on improving food safety, **3.** To ensure advances in medical product safety by "building safety considerations into every aspect of product development," with close postmarket monitoring, **4.** To foster industrial innovation, striving to appropriately balance this with regulation, **5.** To assure accountability. "Responsibility to ensure the integrity of our food and drug supply is a shared responsibility throughout the lifecycle of a product."

## » Sponsored links, now Cheerios... a crackdown?

Last month 14 drug marketers were cited for sponsored links on Internet search engines. Last week, Sanofi-Aventis was hit with an untitled letter over a study reprint involving Taxotere. And now General Mills has been cited for making health claims on Cheerios cereal boxes that the agency says cause it to be an unapproved drug. As the Obama administration and new FDA leadership set up shop, can all this be a precursor to what many have predicted — a crackdown on marketing practices? It certainly does seem there is increased FDA enforcement going on in the marketplace, reversing years of decline under the Bush administration. Warning and untitled letters this year are on pace to eclipse previous annual averages (albeit 14 letters issued on the same day on sponsored links do skew the numbers). Just the same, product marketers should see this activity as a shot across the bow and realize that now is not the time to push the envelope.

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## Hearing divided on bill to reverse Riegel

The U.S. Supreme Court's PMA device pre-emption ruling in *Riegel v. Medtronic* gives consumers the "worst of both worlds," Georgetown University law professor **David Vladeck** told a House Energy and Commerce Committee Health Subcommittee hearing 5/12. "On one hand, FDA cannot single handedly assure the safety of the thousands of medical devices on the market today... On the other hand in the aftermath of *Riegel*, patients injured by devices are left with no remedy in the law... Making matters worse, manufacturers have little economic incentive to swiftly recall devices or repair defective devices on the market since they are immunized from liability and tort." However, former FDA chief counsel (Carter Administration) and now-partner at Williams & Connolly **Richard Cooper** argued that the "su-

premacy of federal law over state law, operating through the doctrines of express or implied preemption, is fundamental to our federal system." He warned that without preemption, each state would apply their own body of law and regulations to impose additional requirements on device manufacturers.

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## » 510(k) route to market under new attack

Two new pointers to the inadequacy of Sec. 510(k) to protect public health and safety emerged last week in a *New York Times* exposé of vaginal sling toxicity and new medical literature reporting elevated safety issues with new ophthalmic lasers. Both devices, substantially different from the "predicate" devices they referenced in their "substantially equivalent" 510(k) submissions to FDA, are now the subjects of liability or malpractice lawsuits. They add to a growing list of earlier examples of problems with 510(k) reviews in CDRH that cited other devices and are currently under Congressional scrutiny. One, ReGen Biologics' Menaflex, is the focus of an internal FDA re-examination ordered by acting commissioner **Joshua Sharfstein**.

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## » Lupin slapped with Warning Letter

Lupin is the latest Indian drug maker to find itself in FDA's crosshairs after being issued a Warning Letter this month over GMP problems documented during an 11/08 inspection at the firm's generic cephalosporin manufacturing facility in Mandideep, India. Fifteen procedural observations were noted on the FDA-483, according to the company. Lupin says it responded to the observations 12/08 and proposed corrective actions for each finding. However, the letter took exception to some of the responses and requested additional documentation and explanations. Lupin management indicates that the letter does not affect the approval and marketing status of any currently approved product. It also does not expect manufacturing to be disrupted.

## » GMP Warning Letters show bad response

A just-released Hogan & Hartson analysis of more than 25 good manufacturing practices (GMP) Warning Letters issued by FDA in the last 12 months shows that almost all of them addressed inadequacies in the company's inspection response. "While there are a variety of acceptable ways to

### LATEST WARNING LETTERS

Brymill Corp. (2/18) — device  
Elkhart General Hospital (5/6) — blood  
Mainline Technology, Inc. (1/23) — device  
Nostrum Laboratories (4/27) — drug  
Samglo Enterprises (5/7) —  
Susan Ambrosino's Herb Club (5/4) — drug  
www.extremeimmunity.com (5/6) — drug

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respond to an inspection observation," the analysis says, "we have seen many examples of inspection and Warning Letter responses that fail to adequately address FDA's concerns." Written responses, Hogan & Hartson says, should demonstrate a commitment to manufacturing high quality drug products and to implementing aggressive corrective action as part of a robust quality system. [Read More](#)

» **FDA's Goodman urges more transparency**

FDA chief scientist **Jesse Goodman**, who was recently named acting deputy commissioner for scientific and medical programs, said 5/18 he has been struck at how the public sees much of the government as less than transparent, "But FDA, I think is particularly opaque at times." Speaking to the FDA Science Board, Goodman said, "It's not that there are bad people who want to be opaque." But, he said, it's that the agency deals with a complex system of laws, regulations, and protections that "make it seem like a black box. But I think that getting beyond this is very important." "You can't change it all. But it's a value and an attitude that we want to change," he said. "I think the reason to change this is that we will have better decisions and more trust" if the agency has the right input and can explain what it's doing in a way people can understand. Stressing that even the scientists don't understand everything about issues of risk, he said, "But I do think more transparency will increase confidence and trust. It won't always be easy, but it is the right way to go." [Read More](#)

» **Science Board endorses pathogen detection**

FDA's Science Board 5/18 unanimously endorsed a report saying the agency's science projects that are of highest priority and are important to a number of its enters are those related to rapid pathogen detection; to pathogen detection and elimination in manufacturing and in products; and to more rapid and efficient detection of adverse events. That "A" list includes, for example, CDER's Sentinel System Project currently under development for medical products adverse events analysis using a distributed network. The report, written by a subcommittee of the board, reviewed summaries of 32 projects from all the FDA centers. According to board member **David Parkinson**, who is president of Nodality, Inc., and who headed the subcommittee, the projects in the report's "B" category are also high priority: "It would be hard to de-prioritize them." However, he explained, they are projects related to the mission of individual centers.

» **21 antiepileptic drugs get suicide warning**

Labeling for 21 antiepileptic drugs was changed 4/09 to include a new Warning on suicidal behavior and ideation. The labeling change also includes a Warning on pregnancy usage and a Precaution encouraging patients to enroll in a pregnancy registry if they become pregnant. The MedWatch listing of changes includes these antiepileptics getting the new labeling: Carbatrol, Celontin, Depakene, Depakote, Dilantin-125, Equetro, Felbatol, Gabitril, Keppra, Klonopin, Lamictal, Lyrica, Mysoline, Neurontin, Peganone, Stavzor, Tegretol,

**ADVISORY COMMITTEE UPDATE**

Latest results ...

Members of FDA's Plastic and Reconstructive Surgeries Devices Panel voted 4-0 to recommend expanding the indication for Covidien's DuraSeal Xact Sealant System for use in patients undergoing spine procedures. FDA had told the panel it found no significant safety problems in the new indication. While voting to recommend approval of the new indication, panelists expressed some concerns about the product, suggesting that there is no clear difference in fluid leakage 90 days post-surgery, although clinical data show that DuraSeal works better than other incision closure methods during surgery itself. The panelists also recommended that if FDA approves the indication, it should require the company to collect additional data.

Tranxene, Tridone, Trileptal, and Zarontin.

» **FDA reports 86 rules in process**

FDA lists 86 rules in process in the HHS section of the Spring 2009 Agency Rule List shown online as part of the Unified Agenda and Regulatory Plan. Included are two items in the pre-rule stage, 22 in the proposed rule stage, 27 in the final rule stage, 28 listed as long-term actions, and seven shown as completed actions. Among items shown as completed actions are IRB registration requirements, requirements for submitting in vivo bioequivalence data, and Patient Safety and Quality Improvement Act of 2005 rules. Long-term actions include review of 12 types of OTC products and post-marketing safety reporting requirements for human drugs and biologics. Items in the final rule stage include cGMPs for positron emission tomography drugs and additional safeguards for children in clinical investigations.

» **Baxter finds no heparin quality problems**

Baxter Healthcare says three adverse patient events at Delaware's Beebe Medical Center were not related to product quality involving the firm's heparin premix products. Baxter and FDA were notified 5/8 of adverse events involving three patients who experienced intracranial bleeding. "Following extensive product testing and further medical evaluation, we are confident that the events at Beebe Medical Center are unfortunate, isolated, institution-specific issues, unrelated to the quality of Baxter's heparin premix product," said Baxter Pharmaceuticals and Technology general manager **Camille Farhat**. A company statement said the investigation covered the supply chain, including raw materials, and it was found to meet all requirements. Evaluation of the medical information received indicated that the product performed as expected and that the intracranial bleeding was related to underlying medical conditions and risk factors that increase the relative risks involved in using a particular drug, Baxter said.

» **Justice Dept. and 16 states go after Wyeth**

The U.S. Justice Department and 16 states have joined in two whistleblower suits filed in Massachusetts against Wyeth over allegations that the company knowingly failed to give the government the same discounted prices that private purchasers paid for drugs as required under the Medicaid "best price" program. Wyeth allegedly avoided paying hundreds of millions in rebates owed to state Medicaid programs for proton pump inhibitors Protonix Oral and Protonix IV, which are used to suppress stomach acid.

**LATEST FEDERAL REGISTER NOTICES**

5/13 Notice: FDA is making available a compliance guidance for small business entities entitled "Labeling OTC Human Drug Products; Small Entity Compliance Guide"

5/14 Notice: Guidance available: *Animal Generic Drug User Fees and Fee Waivers and Reductions*

5/14 Notice: FDA has determined the regulatory review period for Amgen's Sensipar (cinacalcet HCl) is 2,089 days

5/14 Notice: Determined that 10 drug products were not with drawn for reasons of safety or effectiveness

5/15 Notice: Meeting: Pediatric A/C: 6/23

5/15 Final rule: Approval of an American Pharmaceuticals and Cosmetics, Inc. ANADA that provides for the veterinary prescription use of gentamicin sulfate and betamethasone valerate topical spray in dogs for treating infected superficial lesions in dogs

5/19 Notice: FDA is withdrawing approval of 92 NDAs and 49 ANDAs from multiple applicants

5/19 Notice: Submitted to OMB: Medical Device Reporting: Manufacturer, Importer, User Facility, and Distributor Reporting —21 CFR Part 803

5/19 Notice: The meeting of the Gastrointestinal Drugs A/C scheduled for 5/20, is cancelled. FDA continues to review the application that was going to be discussed