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INSIDE THIS ISSUE

FDA Mandates Postmarket Studies, Label Changes for ER/LA Opioids

Drugmakers with FDA-approved NDAs for extended-release and long-acting (ER/LA) opioid painkillers will be required to conduct postmarketing studies to help the agency better understand the "epidemic" of abuse and misuse of the drugs, FDA Commissioner Margaret Hamburg said Sept. 10.

Drugmakers will be required to conduct clinical trials and collect data over a twelve-week period, with the hopes of gleaning information to inform future regulatory decisions about ER/LA opioid painkillers by the end of 2015, Douglas Throckmorton, CDER's deputy director of regulatory programs, said.

The FDA is requiring the studies under enhanced authorities granted as part of the Food and Drug Administration Act of 2007. The studies will only be required for NDA-holders of these drugs, not ANDA sponsors, according to the agency.

(See **Opioids**, *Page 6)*

House Lawmakers Inch Toward Bipartisan Accord on Compounding Pharmacy Reform

A bipartisan group of House lawmakers introduced legislation Sept. 12 proposing new federal requirements for large compounding pharmacies, signaling a potential breakthrough on the contentious issue.

H.R. 3089, the *Compounding Clarity Act*, is intended to clarify the FDA's existing authority over large-scale compounders who mix drugs without a prescription and ship them to other states. The bill was introduced by Rep. H. Morgan Griffith (R-Va.) and co-sponsored by Reps. Gene Green (D-Texas) and Diana DeGette (D-Colo.).

The bill is largely similar to a draft that Griffith floated earlier this year (*WDL*, July 1).

The only major change is the addition of new federal requirements rendering large compounders subject to "annual registration; reporting and listing of the drugs they compound; labeling; adverse

(See **Compounding**, *Page 8)*

Revised GDUFA Guidance Clarifies Packager & Fatal Flaw Definitions

Companies that package an approved ANDA product for the first time are classified as a packager subject to GDUFA's facility fees, the FDA says in newly revised GDUFA question-and-answer guidance.

The agency's update to the August 2012 document follows the Sept. 4 public shaming of facilities that failed to submit their annual facility fee required under the Generic Drug User Fee Act (*WDL*, Sept. 9). The FDA's arrears list included a handful of pharmaceutical packaging companies as well as a number of active pharmaceutical ingredient (API) manufacturers that may have been unaware of their requirements under the new law.

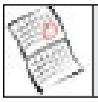
Repackagers and quality control testing sites are not required to pay facility fees under GDUFA.

The initial draft guidance sparked industry comments about the definition of a "fatal flaw," which the FDA defines as "a serious and rare occurrence that requires an ANDA sponsor to manufacture a new demonstration batch of its product or to conduct a new bioequivalence or clinical study" (*WDL*, Aug. 27, 2012). The update clarifies that discovery of a fatal flaw is the "only" thing that will bring all review activities, including compliance inspections required for drug approval, to a halt.

Fiscal 2013 marked the first year of the FDA's generic-drug user fee program, authorized by the FDA Safety and Innovation Act. In addition to clarifying questions on facility fees, the revised guidance also sheds some light on questions related to drug master files, ANDAs and prior approval supplement fees and other fee questions such as payment processes and reimbursements.

The guidance also details what types of facilities need to self-identify, what information will be required, how to submit such information and penalties for noncompliance.

Comments on the revised draft are due Nov. 12. View it at www.fdanews.com/ext/files/09-11-13-GDUFA.pdf. — Nick Otto



FDA CALENDAR

Upcoming meetings through Sept. 25:

- Sept. 16-18: PDA/FDA Joint Regulatory Conference. Washington, D.C.
- Sept. 18-19: PDA/FDA Improving Investigations Workshop. *ICH Q10 Workshop Series*. Washington, D.C.
- Sept. 24: Public meeting on patient-focused drug development for narcolepsy. Silver Spring, MD.
- Sept. 25: The Pharmaceutical Science and Clinical Pharmacology Advisory Committee will discuss strategies for the evaluation, interpretation and communication of drug-drug interaction information. Bethesda, Md.

Comment deadlines through Sept. 30:

- Sept. 30: Comments due on the draft guidance *Antibacterial Therapies for Patients with Unmet Need for the Treatment of Serious Bacterial Diseases*, docket no. FDA-2013-D-0744-0001.

FDA FOIA LOG

The FDA received 161 FOIA requests the week of Aug. 5 including the following.

View the complete FOIA log for the week of Aug. 5 at www.fdanews.com/ext/files/09-11-13-FOIALog.pdf.

Date	Requester	Requested Information
8/6/2013	Sanofi	Establishment inspection report for Jost Chemical Company's Breckenridge Hills, Mo., facility.
8/8/2013	Janssen	Form 483 for Luitpold Pharmaceuticals' Shirley, N.Y., facility.
8/9/2013	Dr. Reddy's Laboratories	Summary basis for approval for ACS Dobfar Info SA's zoledronic acid.

Hamburg Says Healthcare 'Ecosystem' Reform Triggered FDA Streamlining

Speaking to a group of industry stakeholders Sept. 12, FDA Commissioner Margaret Hamburg said a recent call to streamline the agency should be seen as part of a national "comprehensive strategy" to overhaul the healthcare system.

"There really is an ecosystem here and we have to, as a nation, address the challenges before us as an integrated whole with a real comprehensive strategy," Hamburg said. "We have to look at economic policies, we have to look at reimbursement policies and we have to look at regulatory policies and pathways."

Hamburg said she has been in talks with the White House and other key stakeholders to develop such a strategy. "It's much bigger than the FDA," she added. "My goal as FDA commissioner is to help make sure we are delivering on the promises of science and technology, and today I see this as part of my mission even though many of the pieces of this ecosystem ... are far outside our area of activity."

Hamburg has asked center heads to develop ideas to streamline the agency and submit their ideas to her in the next three months (*WDL*, Sept. 9).

Speaking on a panel at Research America's 2013 National Health Research forum in Washington, D.C., Hamburg said she hopes they will present ideas that will include ways to improve regulatory science. Ultimately, she hopes they will find ideas to streamline the way the agency reviews product applications and modernize their business practices so they are better able to communicate with industry about FDA requirements.

(See **Hamburg***, Page 4)*

Johnson & Johnson Beset by Recalls Again

Johnson & Johnson (J&J) continues to suffer from quality issues, experiencing a recent pair of high-profile recalls concerning problems with both prescription and OTC drug products.

J&J's OTC subsidiary McNeil Healthcare on Sept. 9 issued a recall of about 200,000 bottles of children's Motrin (ibuprofen) due to potential plastic particulates. Then just two days later, J&J recalled one lot of its antipsychotic Risperdal Consta (risperidone), which a spokeswoman for the company told *WDL* was contaminated with mold that is "commonly found in the environment."

The company pulled 5,000 vials of the antipsychotic, a long-acting injectable form of risperidone administered every two weeks by a healthcare professional. The recall does not affect the oral version of Risperdal.

The risk for patients is "considered low," the spokeswoman said. There have been no adverse events of infection reported with the troubled lot, she added.

The drugmaker blames tainted supplies of ibuprofen for the children's Motrin recall, saying tiny plastic particulates about the size of a poppy seed were found in a different, unreleased product lot during manufacturing.

"McNeil has worked with the third party to ensure that corrective measures are currently in place and are effective," the company said. The likelihood of adverse events arising from particles is "not likely," it added.

Previous Predicaments

J&J quality issues have previously prompted regulatory enforcement. The state of Oregon sued McNeil and J&J a few years ago over a "phantom recall" of Motrin, alleging McNeil failed to notify retailers and consumers of possibly defective products and tried to "quietly remove Motrin containers from store shelves" (*WDL*, Jan. 17, 2011).

McNeil continues to operate under a consent decree it entered into a few months after the lawsuit was filed. The decree brought an end to one

(See **J&J***, Page 4)*

Novartis Boosts Cell Therapy Portfolio in Licensing, R&D Deal

Looking to pump up its cell therapy portfolio, Novartis Sept. 6 revealed plans to partner with Kentucky-based Regenerex for use of the company's facilitating cell therapy (FCRx) platform.

The hematopoietic stem cell-based platform has already been investigated in kidney transplantation to induce stable immunological tolerance. Specifically, FCRx is used to develop "bone marrow chimerism" in transplant recipients, ultimately providing a better side-effect profile than current treatment, its creator says. Chimerism may eventually allow a patient to tolerate cell, tissue or organ transplants from the same donor, thereby enabling transplant patients to discontinue immunosuppressive drugs after building stable immunological tolerance.

Novartis says the FCRx platform has remedial potential for multiple diseases and will be investigated in the use of serious genetic deficiencies such as inherited metabolic storage disorders and hemoglobinopathies.

Novartis' pre-collaborative cell therapy pipeline includes HSC835, an approach — currently in Phase II studies — that enables stem cell transplants based on blood derived from umbilical cords in patients with limited treatment options. A second product is CTL019, a chimeric antigen receptor T cell therapy, also in Phase II, to treat acute lymphoblastic leukemia and chronic lymphocytic leukemia. — Nick Otto

J&J, *from Page 3*

of McNeil's three U.S. facilities. Production volume at its remaining plants in Lancaster, Pa., and Las Piedras, Puerto Rico, has been negatively impacted by the decree's requirement that a third party review records for selected batches, according to J&J's 2012 annual report.

The recalled Motrin was manufactured at J&J's Beerse, Belgium, plant, a McNeil spokesperson told *WDL*. The representative declined to reveal the ibuprofen supplier.

The recalls are a hiccup in J&J's efforts to restore consumer confidence in its OTC brands. That effort is being led by former Bayer exec Sandra Peterson, who took over as head of J&J's consumer group business in December.

During a July 16 conference call to discuss J&J's second quarter earnings, Peterson said OTC remediation is expected to continue apace in the near-term, and that the drugmaker expects to deliver a "reliable and consistent supply" of three-quarters of its OTC brands by the end of the year.

Despite the manufacturing setbacks, J&J's OTC segment continues to be profitable. U.S. sales of OTC drugs reached $290 million in the second quarter of 2013, reflecting a 17-percent increase over the same quarter in 2012.

The recall comes in the midst of heightened FDA scrutiny on supplier oversight. The agency released draft guidance earlier this year providing recommendations on how companies can craft a quality agreement with a contract manufacturer (*WDL*, June 3). — Robert King

Hamburg, *from Page 3*

"We have actually supported a lot of work externally and in partnership with industry and academia and done a lot internally to really look at how can we develop really innovative clinical trial approaches, how can we decrease the time clinical research needs to be done," added Hamburg.

Hamburg told *WDL* she is also concerned with the FDA's ability to conduct inspections on the ground. She said historically, FDA investigators have had to cover a wide range of inspections, but "in the modern era" the experience and training needed to properly do inspections are very different. "We're trying to really modernize, professionalize, better utilize staff and provide ultimately better service to our stakeholders in terms of the job we do," added Hamburg. "So we're looking at how we can better organize and train staff." — Ferdous Al-Faruque

ISPE Works With Industry, FDA To Establish Metrics

The International Society for Pharmaceutical Engineering (ISPE) is searching for common ground between the FDA and industry on quality metrics, which the agency believes can improve drug quality and drugmakers contend will only cause confusion.

The association announced the quality metrics project in the Sept.-Oct. issue of its journal *Pharmaceutical Engineering*. The goal is to develop a white paper acceptable to industry and regulators that defines objective metrics for use in a risk-based inspection program.

Prompted by new legislative mandates for more risk-based inspections, the FDA recently asked drugmakers to share their methods for measuring manufacturing quality, and asked whether such "metrics" should be used to guide patients and prescribers in their product choices (*WDL*, Feb. 18). Some commenters said such metrics are "internal" tools that, if applied globally to guide consumer choices, would upend drug markets.

The project started during a June ISPE conference where attendees at a workshop voiced lingering questions about the challenges surrounding quality metrics, including:

- Should they be measured by site, product or company?
- Does the metric truly reflect quality and/or compliance? and
- Would their wider use lead to unacceptable behavior by industry or regulators?

After reviewing the feedback, ISPE decided to focus on quality metric topic areas that include out-of-specification failure investigation rates and batch failure rates.

The idea is for industry leaders to first test any metric suggestions developed by the ISPE and then allow the agency to discuss them. An update on the project will be given at the association's annual meeting in November in Washington, D.C. The association plans to publish the white paper sometime after the meeting.

The group said it understands the challenges it faces reaching consensus between industry and the FDA. "Nonetheless, there is enthusiasm to move forward and explore what practical and acceptable quality metrics could be developed which are useful to industry and regulators," the association says. — Robert King

Funding Issues Force FDA to Cancel Data Mining Project

Funding woes have forced the FDA to cancel a data mining project it hoped would help the agency find adverse event trends faster.

The agency posted a notice to the Federal Business Opportunities (FBO) website in April, seeking proposals from contractors capable of creating a program to glean safety signals from the National Library of Medicine's MEDLINE database of biomedical abstracted articles and citations.

The "automated and fully auditable commercial off-the-shelf software product" would also have been integrated with the agency's current data mining software, dubbed Empirica Signal, which mines for safety signals in the FDA Adverse Event Reporting System (FAERS).

The FDA has sought to improve its adverse event reporting and data mining techniques ever since a subcommittee of the Science Board said last year that the agency needed to create an integrated approach to data mining, rather than the current fragmented one. The subcommittee had been assigned to review CDER's pharmacovigilance program (*WDL*, May 23, 2011).

The new data mining program was expected to be sophisticated enough to "efficiently distinguish real signals from the background noise in huge pharmacovigilance databases," the April notice said.

But earlier this month, the FDA posted a single line to update its request, saying "due to lack of funding, the requirement has been cancelled."

The FBO notice can be viewed at www.fdanews.com/ext/files/09-11-13-FBO-Notice.pdf. — Melissa Winn

FDA Exceeds GDUFA Hiring Goal

The FDA has not only met but exceeded its Fiscal 2013 hiring goal, bringing on board 234 new employees, CDER Director Janet Woodcock said in an internal memo to staff Sept. 11.

The target of 231 hires is an agency-wide congressional mandate, Woodcock said. It is based on the agreed number of total hires for the entire GDUFA hiring initiative, lasting until September 2015, she added. The overall goal is 921 hires, divided over three years with a 25–50–25 percent split for years one, two and three, respectively. — Melissa Winn

FDA Expands Celgene's Abraxane For Late-Stage Pancreatic Cancer

The FDA Sept. 6 approved a new indication for Celgene's Abraxane to treat patients with late-stage pancreatic cancer, an outcome prompted under priority review and orphan drug programs.

Specifically, the drug is now approved as a first-line treatment for patients with metastatic adenocarcinoma of the pancreas, in combination with gemcitabine. Adenocarcinoma, a sub-type of exocrine tumors, accounts for about 95 percent of cancers of the pancreas, Celgene says.

The safety and efficacy of Abraxane (paclitaxel protein-bound particles) for pancreatic cancer were established in a clinical trial of 861 patients who were randomly assigned to receive Abraxane plus gemcitabine or gemcitabine alone.

Participants treated with Abraxane plus gemcitabine lived, on average, 8.5 months, compared with 6.7 months for patients who received standard therapy of gemcitabine alone. Additionally, participants who received Abraxane plus gemcitabine experienced a 1.8-month progression-free survival compared to those receiving just gemcitabine.

Common side effects included a decrease in white blood cells, a low level of platelets in the blood, fatigue, arm and leg nerve damage, and nausea.

Abraxane was first approved in 2005 to treat breast cancer, and later received an additional indication for lung cancer. Abraxane is currently under study as a first-line treatment for breast cancer and melanoma, according to Celgene's website. — Nick Otto

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Opioids, *from Page 1*

The FDA expects the sponsors will develop parameters for the studies that will then be discussed with the agency, Throckmorton said during a conference call announcing the new requirements, which also included class-wide safety labeling changes.

The labeling changes, which include an updated indication for use and changes to the patient counseling information and medication guide, will be required of all manufacturers of ER/LA opioid painkillers. The modified indication for use has eliminated the use of the word "moderate." It states ER/LA opioids "are indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate."

"This new labeling language emphasizes that patients in pain should be assessed not only by their rating on a pain intensity scale, but also based on a more thoughtful determination that their pain — however it may be defined — is severe enough to require daily, around-the-clock, long-term opioid treatment, and for which alternative treatment options are inadequate," the agency said in a consumer alert on the changes.

The labeling changes "will encourage better, more appropriate, prescribing, monitoring and patient counseling practices involving these drugs," Throckmorton said.

To view a sample of an FDA letter to sponsors outlining the new postmarketing requirements, go to www.fdanews.com/ext/files/09-10-13-opioid-studies.pdf. — Melissa Winn

OIG Says Medicare Drug Rebates Could Save Billions; CMS Disagrees

If drugmakers were required to pay rebates on Medicare Part B drugs, similar to those they pay for Medicaid drugs, Medicare could save billions of dollars a year, according to a recently published study by the HHS Office of the Inspector General (OIG).

Under one scenario, Medicare could have collected $3.1 billion if drug manufacturers had been required in 2011 to pay rebates for 60 high-expenditure Part B drugs, according to the report. The savings would represent 22 percent of Medicare spending on the drugs, it adds.

The report, requested by former Sen. Herb Kohl (D-Wis.), recommends the Centers for Medicare & Medicaid Services (CMS) examine the idea of establishing a prescription drug rebate program under Medicare Part B and, if appropriate, "seek legislative change."

Although Medicare Part D covers most outpatient prescription drugs, Medicare continues to cover a limited number of drugs under its Part B benefit, including certain injectable drugs and some vaccines and oral anticancer drugs.

Despite the seeming windfall of funds, the CMS doesn't like the idea, saying the study "did not estimate the administrative costs of implementing and maintaining such a program, nor the impact on healthcare providers, drug manufacturers, or beneficiaries."

Such a move would have "a very negative impact on innovation" and might also very well lead to drug shortages, Peter Pitts, president of the Center for Medicine in the Public Interest and a former FDA associate commissioner, told *WDL* Sept. 11. These are only two of the "negative unintended consequences that occur when cost is put in front of patient care," he added.

The full report on the study can be viewed at www.fdanews.com/ext/files/09-11-13-Part-B.pdf. — Melissa Winn

Sanofi Pipeline Snagged Again As Company Pulls Diabetes Drug NDA

French drugmaker Sanofi said Sept. 12 it has withdrawn its NDA for its once-daily Type 2 diabetes treatment lixisenatide, citing complications with interim cardiovascular (CV) data.

The FDA accepted the NDA for review in February. Sanofi now says it will have to wait until 2015.

The withdrawal decision follows discussions with the agency that led Sanofi to believe potential leaks of sensitive and interim data could "compromise the integrity" of its ongoing ELIXA study of the drug's CV risk, it said. Complete trial results won't be available for another 15 months.

The "most appropriate" option is to support the FDA's evaluation of lixisenatide based on the complete results of the ELIXA study, rather than incomplete interim data, the company said.

The drug has already been launched in Europe under the brand Lyxumia to treat Type 2 diabetes.

As the NDA withdrawal was not associated with negative safety/efficacy data, investors remain upbeat about emerging glucagon-like peptide 1 (GLP-1) diabetes therapies, Leerink Swann analyst Seamus Fernandez said in a research note Sept. 12.

The NDA withdrawal is the latest blow to the company's dwindling drug pipeline this year.

Results from two Phase III trials that came in over the summer showed investigational drugs iniparib for lung cancer and the anticoagulant otamixaban were no more effective than current standards of care. Sanofi abandoned the development programs for both drugs (*WDL,* June 10).

Earlier this year, the drugmaker ceased development of two other pipeline projects: sarcoma drug ombrabulin and endometrial cancer drug SAR245408.

LixiLan, also used for the treatment of diabetes, "remains on schedule" to enter into Phase III in the first half of 2014, Sanofi noted Sept. 12. LixiLan is a combination of lixisenatide and Lantus (basal insulin). — Melissa Winn

Éclat Wants FDA to Pull 'Unapproved' Injectables

Éclat Pharmaceuticals is calling on the FDA to stop five of its competitors from selling certain injectables that the specialty drugmaker claims are unsafe and unapproved drugs.

St. Louis, Mo.-based Éclat complains in a citizen petition that the five companies — Cardinal Health, West-Ward Pharmaceuticals, Fresenius Kabi USA, American Regent and General Injectables & Vaccines — are marketing unapproved versions of its Bloxiverz (neostigmine methylsulfate) injection, approved in two doses back in May.

The FDA has indicated that when a drugmaker obtains approval of an NDA for a product that others are marketing without approval, "the removal of the unapproved versions becomes a priority," Éclat says in the Aug. 15 petition, which was posted Sept. 4.

Éclat also claims the copycats lack complete labeling and pose a potential safety hazard.

Patients could be significantly under-dosed without the specific recommendations that the agency signed off on for Éclat's product, leading to residual neuromuscular blockade and other complications, the company said.

To read the petition, visit www.fdanews.com/ext/files/09-05-13-EclatPetition.pdf. — Robert King

Compounding, *from Page 1*

event reporting; inspections and user fees," according to a press release.

The requirements are similar to those contained in S. 959, the *Pharmaceutical Quality, Security and Accountability Act*, which combines compounding reform with the creation of a nationwide pharmaceutical track-and-trace system (*WDL*, July 22). That bill has cleared the committee process and currently awaits a vote on the Senate floor.

While the legislation appears to grant the FDA new authority, a source familiar with the legislation told *WDL* that Griffith still sees this bill as clarifying the agency's existing powers. The legislation keeps regulation of traditional pharmacies at the state level.

The bill comes on the heels of the one-year anniversary of a fungal meningitis outbreak linked to contaminated drugs mixed at the New England Compounding Center (NECC) (*WDL*, Oct. 22, 2012).

The FDA told Congress in subsequent hearings that it needed new authority to find and inspect larger compounders such as the NECC (*WDL*, April 22). House Republicans previously balked at such a demand, noting that the agency has inspected more than 50 pharmacies in the wake of the outbreak (*WDL*, April 29).

The bipartisan legislation could mean renewed momentum in the House. The bill is part of ongoing behind-the-scenes talks between House and Senate staff on merging compounding legislation, the source familiar with the legislation said.

However, it remains unclear if this will be the only bill to emerge from the House Energy & Commerce Committee, the source said. Other House Democrats have introduced legislation on the issue. However, Committee Chairman Fred Upton (R-Mich.) and Vice Chairman Marsha Blackburn (R-Tenn.) lauded Griffith's bill as a positive step.

Griffith's bill has already received an endorsement from one pharmacy trade group, with the National Community Pharmacists Association swiftly reiterating its support. The International Association of Compounding Pharmacists, which represents the nation's larger compounding pharmacies, gave a more measured response.

The trade group believes Griffith's bill offers "a significant improvement over the Senate bill," spokesman David Ball told *WDL*. "There are some issues that will need to be resolved, including those that pertain to federal vs. state authority, and we are eager to begin that process."

To read H.R. 3089, visit www.fdanews.com/ext/files/09-12-2013-House-Compounding-Bill.pdf. — Robert King

FDA Criticized for Dropping Human Trial Requisite for Restasis Generics

The FDA should explain why it has decided to nix the need for human studies to demonstrate bioequivalence to Allergan's dry eye treatment Restasis, according to a slew of comments and letters posted online in response to agency draft guidance on the subject.

The letters come from a variety of commenters, not just from the drug's maker, which issued a 43-page response to the guidance in support of its innovative product.

The guidance, posted earlier this month, is a "significant departure from the agency's longstanding policies and practices regarding bioequivalence for complex ophthalmic treatments," say more than a dozen patient advocacy groups, including the American Autoimmune Related Diseases Association, Prevent Blindness America and the Alliance for Patient Access.

Generic emulsions, especially for topical drops used to treat dry eye (such as cyclosporine emulsions) must be evaluated with the same human trials as Restasis (cyclosporine ophthalmic emulsion), Mark Milner, Yale University, argues. Generic drops have the same active ingredient, he says, but may have different vehicles and/or preservatives that could affect the eye negatively.

It's "crucial" that generic emulsions be held to the same standards with human studies to ensure "we are improving the surface of the eye and not compromising it," Milner adds.

Allergan echoed those comments, saying that until now, the FDA has recognized that the only "scientifically valid way to demonstrate that a proposed generic drug is bioequivalent to an ophthalmic emulsion" such as Restasis is to conduct comparative clinical trials to demonstrate equivalent safety and effectiveness based on clinical endpoints.

Several of the nearly two dozen comments the agency received before the comment period closed in August challenged the agency to explain what scientific evidence supports its determination that laboratory studies alone can establish bioequivalence.

The patient advocate groups also complained that the FDA did not develop the draft guidance with enough transparency. The process, they said, "did not invite input from the provider and patient community." Such collaboration is "essential to adequately address both the complex science of emulsions, and the potential impact on patient safety," they added.

An FDA spokesperson would not comment on the particulars of the guidance and told *WDL* Sept. 12 it was "premature" to say what changes may be made to it.

Restasis was approved in 2002 for the treatment of chronic dry eye. A patent protecting the drug from copycat versions expires in 2014.
— Melissa Winn

Comings & Goings

Former FDA Commissioner **Frank Young** has joined the management team of Braeburn Pharmaceuticals as its executive vice president, clinical and regulatory affairs. Young served as FDA commissioner from 1984 to 1989, during the Reagan and Bush administrations.

NPS Pharmaceuticals' president and chief executive officer **Francois Nader** has been appointed to the Biotechnology Industry Organization's (BIO) board of directors as a member of the Health Section Governing Board.

Brenton Saunders, the former chief executive officer of Bausch and Lomb, has been appointed Forest Laboratories' new chief executive officer and president, effective Oct. 1, 2013. Saunders will succeed **Howard Solomon**. Solomon will remain non-executive chairman of the board through Forest's 2014 annual shareholders meeting, when Saunders is expected to become chairman of the board.

THE BUZZ

Hans-Georg Eichler, senior medical officer at the European Medicines Agency (EMA), has been a major player in the agency's push for more trial transparency. As someone who's worked in pharma as well as academia, Eichler has a breadth of knowledge about the industry, which he is using to help the EMA develop a nuanced approach to transparency that protects patients and takes into consideration industry interest.

***WDL**: We've been following the EMA's transparency initiatives and those of the FDA. Do you see the agencies lining up their initiatives and where do you see differences between them?*

The obvious difference is that we operate in a different legal environment and we also operate in a different political climate. I would think this push for transparency at this point in time is much further along in Europe because you have the AllTrials campaign and you have a lot of public advocates for open trials. I think it's more at center stage in Europe than it is in the U.S.

I don't know if we are aligned or will be aligned, what I can tell you is we keep each other informed. As with so many other topics between the FDA and EMA, we have teleconferences so they are fully aware of what we do and we are fully informed of what they do.

***WDL**: Do you think the social media environment and the information age that we are currently living in has an effect on the EMA's trial transparency initiatives?*

Absolutely. [The EMA's] authority was taken for granted 20 years ago and [sometimes] questioned, but not at the scale it is questioned today. Are we going into a more open age and does that affect us? The clear and obvious answer is absolutely yes.

***WDL**: How is the EMA preparing to handle more scrutiny?*

There are two elements to this. One is to be open. I think as an agency we are at the forefront of this. We have gone from a reactive to a proactive role because we understand that a modern society will not tolerate secrecy. Particularly not from an organization like ours which has to act in the interest of public health. We are here to serve the public health and we have no business in being secretive. We understand that and we support that, and we will live with the consequences.

With regard to the consequences, if there is more scrutiny it means we have to keep improving how we communicate why we came to a certain decision and be able to defend that position.

MiMedx Gets Untitled Letter For Unapproved Biologics

CBER handed MiMedx an untitled letter over unregulated biologics, saying its regenerative, human cellular and tissue-based products lack approved BLA or IND applications.

The letter follows a current good tissue practice inspection of the company's Kennesaw, Ga., facility last month. Upon review of the investigators' notes, the center learned that certain products that MiMedx distributes and contract manufactures run afoul of the 1938 FD&C Act and the Public Health Service Act (PHSA), the Aug. 28 untitled letter, posted Sept. 4, states.

Specifically, the products don't meet "the minimal manipulation criterion" of the PHSA, meaning the "original relevant characteristics" of the structural tissue have been altered such that the products are defined as FDA-regulated biologics and not solely regulated under the PHSA.

A July 2012 inspection of one of MiMedx's facilities expressly intended to determine the regulatory status of AmnioFix resulted in a "no action indicated" classification, Bill Taylor, the company's president and chief operating officer, said, expressing surprise at the agency action.

And the formal establishment inspection report confirming that conclusion was issued on Dec. 4, 2012, he added. MiMedx "expressly disagrees" with the FDA, and believes the agency's conclusion is based on a misunderstanding of the micronization process, the company said, adding that it intends to work with the agency to "resolve the matter as quickly as possible."

In a conference call Sept. 5, MiMedx executives downplayed the letter's impact on the company's current revenue guidance for 2013 and 2014.

The untitled letter to MiMedx can be viewed at www.fdanews.com/ext/files/09-05-13-MiMedx-letter.pdf. — Melissa Winn

FDA Advisors Urge Approval of First Preoperative Breast Cancer Treatment

FDA advisors Sept. 12 delivered a resounding recommendation for swift approval of Genentech's sBLA for Perjeta as the first sanctioned preoperative breast cancer therapy.

The FDA's Oncologic Drugs Advisory Committee voted 13-0, with one abstention, to urge approval of Perjeta (pertuzumab) as a neoadjuvant (preoperative) treatment in combination with trastuzumab and docetaxel for patients with HER2-positive, locally advanced, inflammatory or early stage breast cancer. Perjeta is already approved to treat patients with HER2-positive metastatic breast cancer.

Committee members joined agency analysts in noting that the drug shows improvement in fighting early-stage breast cancer and is sufficiently safe. FDA reviewers wanted the committee to meet and discuss the sBLA because Perjeta would be the first preoperative treatment (*WDL*, Sept. 11).

"The short term toxicity is largely similar to the known safety profile of this drug and appears to be manageable," said Suparna Wedam, an FDA medical officer. "If and what long-term toxicities may arise in this curative intent population are not known."

However, the sponsor's primary study in support of its sBLA for Perjeta, NEOSPHERE, didn't sit well with all committee members.

Tito Fojo, National Cancer Institute, who abstained, said the study had too many downsides, including a lack of blinding and no U.S. participants. "At some level I don't think as a committee we can say NEOSPHERE is addressing what we want to address."

The panel's chair, Mikkael Sekeres, Cleveland Clinic Taussig Cancer Institute, emphasized that the drug is being considered for accelerated approval. It offers "a chance to get this drug to people quicker, and I am pretty sure this drug is not going to impose harm on people," he said. The FDA's decision is expected by Oct. 31. — Robert King

FDA Advisors Recommend GSK's COPD Candidate

An FDA advisory panel overwhelmingly recommended approval of GlaxoSmithKline's (GSK) chronic obstructive pulmonary disease (COPD) treatment Anoro Ellipta, but called for a postmarket study and labeling language to address lingering safety concerns.

The agency's Pulmonary-Allergy Drugs Advisory Committee on Sept. 10 voted 11-2 to urge approval of the once-daily drug, which combines the investigational molecules vilanterol and umeclidinium bromide.

The panel's recommendation follows a nod from FDA reviewers, who noted that safety data — based on four primary efficacy trials, a long-term safety study and two exercise endurance trials — raises the possibility of an association between ischemia and the drug.

However, the general safety of the treatment seen in the long-term safety trial, as well as by the low number of cardiac events, helped to ease those concerns.

Many committee members agreed that the safety data wasn't perfect. Committee chair David Jacoby, Oregon Health and Science University, questioned whether patients with more severe cardiovascular disease were underrepresented in the safety study.

"It's hard for me to believe that there is going to be such a low incidence of worsening or congestive heart failure if you are including patients with stage-IV congestive heart failure," said Jacoby.

Other committee members agreed. James Stoller, one of the "no" votes, said there was inadequate data to make a definitive conclusion on the drug's safety risk.

"There certainly is little evidence that makes a definitive statement about the absence of a safety risk, nor is there definitive evidence in favor of a clear-cut safety risk," said Stoller, chair of the Education Institute at the Cleveland Clinic Foundation.

GSK argued that the "data demonstrated no additional risks for the combination therapy," said C. Elaine Jones, the company's vice president of medicine development.

The most common adverse events reported across all study arms were headache, cough, nasopharyngitis, upper respiratory tract infection and back pain, "all of which are common in the general COPD population," said Alison Church, the GSK project leader.

Jacoby and a majority on the committee decided that, despite lingering concerns, the safety studies adequately addressed the signal within the population, paving the way for an overall recommendation.

Many panelists recommended a postmarket study be conducted on Anoro Ellipta's effects on patients with more severe cardiovascular disease, as well as labeling to warn patients with such conditions.

GSK has proposed including cardiovascular risk warning in the product's labeling, Church noted.

Anoro Ellipta has a Dec. 19 PDUFA date.

— Robert King

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