FDA Rolls Out Compounding Guidance, Seeks More Funding

Just days after the FDA’s new authorities over compounding pharmacies were signed into law, the agency last week issued draft guidances detailing how facilities register and report product information to the FDA.

A compounding facility that voluntarily registers with CDER as an outsourcing facility must register annually with the FDA, and twice a year (in June and December) must submit a report identifying the drugs compounded at the facility during the previous six-month period.

Registration of compounders will be handled by CDER through its Drug Registration and Listing System Team. The agency encourages compounders to use its existing drug establishment registration website, but CDER has also laid out an alternative registration option allowing compounders to send registration details via email edrls@fda.hhs.gov.

(See Compounding, Page 8)

Congressional Budget Deal Deadline Quickly Approaching

Congressional negotiators are working to hammer out a new federal budget proposal for fiscal 2014 and fiscal 2015, and a group of lawmakers hopes to use the budget deal to shield FDA user fee revenue from any across-the-board sequestration cuts.

As Congress returns from the Thanksgiving recess, the work of the 29-member bipartisan budget negotiating committee will take center stage. The committee is tasked with coming up with a budget proposal by Dec. 13. Congress, in turn, plans to act before Jan. 15, when the continuing resolution currently funding the government expires.

The negotiating committee — seven house members and 22 senators — formed after lawmakers reached a deal in October to end the 16-day partial government shutdown and temporarily fund the federal government for part of fiscal 2014.

(See Budget, Page 10)
FDA Plans to Study Risk Information in DTC Ads

The FDA plans to launch a study examining how consumers view risk information in direct-to-consumer (DTC) prescription drug advertisements, the latest study delving into how drugmakers craft ads.

The study, which has the potential to affect how advertisers will have to present risk information in ads, will employ eye-tracking technology to determine the impact of visual and audio distractions on understanding risks. The eye-tracking technology will allow researchers to detect and measure what a participant looks at while viewing an ad, the FDA says.

“Previous research has shown that factors such as multiple scene changes and music in advertising can be distracting,” according to a summary of the study published in the Federal Register.

The agency plans to conduct a pilot study with 30 adults, as well as a main study with 300 adults throughout five different cities. All of the participants will be older than 18 and will have expressed a desire to lose more than 30 pounds.

The participants will watch three ads for a prescription weight loss drug, each with different levels of distraction.

This is the second recent study the agency is proposing on how consumers interpret DTC ads. The other study is examining how adolescents process the benefit-risk profile of a prescription drug, which could impact how that profile is communicated in marketing.

The FDA has also stepped up enforcement of misleading or false ads, issuing seven enforcement letters over the past few months.


— Robert King

FDA CALENDAR

Upcoming meetings through Dec. 12:

- Dec. 9: The Gastrointestinal Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee will hold a joint meeting to discuss two BLAs for Entyvio (vedolizumab injection) submitted by Millennium Pharmaceuticals. The first BLA seeks approval of the drug for the treatment of adults with ulcerative colitis. The second proposes to treat certain adults with moderately to severely active Crohn’s disease. Silver Spring, Md.
- Dec. 10: The FDA will hold a public meeting to discuss patient-focused drug development for fibromyalgia. Silver Spring, Md.
- Dec. 11: The Endocrinologic and Metabolic Drugs Advisory Committee will discuss Amylin’s BLA for metreleptin injection for the treatment of metabolic disorders associated with lipodystrophy, including diabetes mellitus and/or hypertriglyceridemia in pediatric and adult patients with inherited or acquired lipodystrophy.
- Dec. 12: The Endocrinologic and Metabolic Drugs Advisory Committee will discuss Bristol-Myers Squibb’s NDA for dapagliflozin, a sodium-glucose co-transporter 2 inhibitor developed as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Comment deadlines through Dec. 23:

- Dec. 9: Comments due on industry guidance Expedited Programs for Serious Conditions—Drugs and Biologics, docket no. FDA-2013-D-0575-0028.
- Dec. 12: Comments due on draft guidance for industry Bioanalytical Method Validation; Availability, docket no. FDA-2013-D-1020-000.
- Dec. 23: Comments due on draft guidance for industry Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Drugs for Treatment, docket no. FDA-2013-D-1170-0001.
FDA Developing Timeline for Track-and-Trace Implementation

With the new pharmaceutical track-and-trace law’s deadline for lot-level pedigrees looming, the FDA is still unclear about how it will regulate the complex requirement.

Guidance on that issue, required under the Drug Quality and Security Act, won’t be rolled out until sometime early next year, even though manufacturers must develop lot-level transaction history for all finished dose forms of prescription drugs by Jan. 1, 2015 (WDL, Nov. 25).

The FDA is developing a schedule for implementing the law’s requirements, which also include scheduling public meetings and developing regulations and standards on the issue, spokesman Christopher Kelly told WDL Dec. 4.

Experts tell WDL the implementation plan, in lieu of concrete recommendations, suggests an admission on the agency’s part that timeframes under the law are “daunting” for both FDA and industry.

The timeline for transaction histories, which document each step a product takes from the maker to the final sale, is the biggest challenge the agency faces on track-and-trace regulation, Vincent Ventimiglia, principal with FaegreBD Consulting, says, citing the need for a standardized way for stakeholders to communicate with each other.

Speaking at a Food and Drug Law Institute meeting, Ventimiglia said drugmakers are clamoring for guidance on the issue.

“That is probably the single biggest challenge that the statute can’t answer,” he said. “Each company will have to find an operational and technical solution.”

More extensive regulations kick in at a later date. For example, within four years, a drugmaker must affix a product identifier to each saleable unit. By late 2017, all stakeholders must adopt an interoperable system that tracks products by unit.

The law includes other deadlines for the FDA to release guidances. By May, the agency must publish draft guidance on how drugmakers can set up a system to identify and quarantine suspect products.

The agency must also hold a public meeting on how a manufacturer can infer that drugs in a large container are what they purport to be. The FDA must then issue guidance 18 months after that meeting.

The law which has been signed into law by President Obama, immediately preempts all state measures on track-and-trace. — Robert King

White House Veers from Proposals To Reduce Biologic Drug Exclusivity

After years of pressure from lawmakers and drugmakers, the Obama administration appears to be surrendering its push for a reduced seven-year exclusivity period for biologic drugs.

Despite recent White House budget proposals advocating the reduced period, administration officials in the latest round of Trans-Pacific Partnership (TPP) trade talks have urged U.S. trade partners to adopt the U.S.’s current 12-year exclusivity period for biologic drugs.

The White House realizes it needs to reach an agreement in the TPP talks, Mark Grayson, deputy vice president of International Public Affairs for PhRMA, told WDL Dec. 4. Every time the administration has asked to change the biologic drug exclusivity period to seven years, “it goes nowhere,” he added.

The administration’s fiscal 2014 budget proposal suggested the earlier introduction of biosimilars to market would save federal healthcare programs $3 billion over 10 years.

The pharmaceutical industry has fought back hard, however, to keep the 12-year exclusivity period granted under the Biologics Price Competition and Innovation Act of 2009.

The industry convinced dozens of members of Congress to write the White House shortly after

(See TPP, Page 14)
Woodcock to Lead Planned Pharmaceutical Quality Office

CDER Director Janet Woodcock has decided to head the FDA’s new Office of Pharmaceutical Quality (OPQ) herself until it gets off the ground. The new office is planned as a “super office” that will oversee manufacturing quality throughout a drug’s lifecycle.

Announced in September, OPQ will take shape sometime next year, and will bring together all FDA drug manufacturing quality functions in one office. The FDA hopes by working more closely, the offices will work more efficiently to oversee global manufacturing and supply sourcing.

Woodcock, who will retain her role as CDER director, will lead the office through its startup and ensure departments work cooperatively during the initial reorganization. At some later time, a permanent director will take charge of the office.

FDA officials have said the proposed OPQ is needed to promote good manufacturing practice standards across all stages of a drug’s lifecycle, and it will be organized into eight sub-offices: Surveillance, Biotechnology Products, New Drug Products, Operations, Policy, Lifecycle Drug Products, Process and Facilities and Testing and Research.


FDA Communications Head, Virginia Cox, to Leave Agency

The FDA’s head of communications Virginia Cox is leaving the agency in January to pursue other opportunities.

Cox has served as the associate commissioner for external affairs since 2011, where she spearheaded the agency’s outreach and communications efforts, the agency said Thursday.

After Cox leaves in January for the undisclosed opportunities, Steven Immergut will become the acting associate commissioner for external affairs. Erica Jefferson, currently the deputy director of strategy in the FDA’s Office of Media Affairs, will take over Immergut’s role as acting assistant commissioner for media affairs. — Robert King

Comings & Goings

Takeda Pharmaceuticals has named former GlaxoSmithKline executive Chris Weber as its new chief operating officer and a candidate for the drugmaker’s next chief executive officer. He is expected to be named CEO in April, when the current CEO Yasuchika Hasegawa leaves.

Glenmark Pharmaceuticals has named former Bausch & Lomb executive Philip Andrew Gioia its president, North America and the global API business.
FDA Cites Pfizer Subsidiary for Lax Oversight, Quality Failures

Pfizer subsidiary Meridian Medical Technologies is under continued pressure from the FDA to improve oversight and quality at its Missouri plants.

The agency has published three 483s it has issued to the company’s plants in St. Louis and Brentwood, Mo., over the last two years, citing them for failing to audit suppliers, inadequate testing of incoming raw materials, poor batch records and other quality problems.

Meridian, a maker of drug auto-injectors, has come under fire from congressmen who are angry about quality deficiencies at the company, which manufactures nerve gas antidote for the Department of Defense.

In a 483 handed to Meridian’s Brentwood, Mo., facility in March, the agency found that an investigation into an out-of-specification result for a diazepam auto-injector product was not thoroughly conducted to detect root cause. The company linked the cause to raw materials, but had not previously audited the supplier. Meridian’s investigation also did not include any testing of supplied diazepam for impurity, according to the FDA.

Meridian also never inspected its contract testing laboratory used to analyze batches for foreign material, the FDA says.

The FDA also faulted procedures used for visual inspections of batches at Meridian’s Saint Louis, Mo., facility, according to a 483 issued in April. At least one visual inspection, intended to ensure there are no missing products, failed to detect missing atropine sulfate injection, the agency said. While the batch was reworked, Meridian did not investigate whether the visual inspection failed for other lots, according to the FDA.

The agency also published a 483 detailing an early 2012 inspection of the Brentwood plant. Investigators found that batch records did not have the actual times manufacturing steps were started and stopped, but rather “theoretical times,” according to the form.

Pfizer is working “in close cooperation with the FDA to address these matters and corrective actions are ongoing,” spokesman Chris Loder told WDL. Loder declined to detail the corrective actions applied.


FDA Wants Wockhardt Management Audited in Quality Data Probe

The FDA wants Wockhardt to investigate whether management was involved in quality data manipulation at its Chikalthana, India, facility before the agency will lift an import ban it slapped on the plant Nov. 26.

The agency Dec. 3 released the warning letter that preceded the import ban, which shows the FDA is concerned that quality data were manipulated and destroyed by plant employees. The agency has instructed the company to audit its data integrity system and determine if individuals responsible for data manipulation are still employed at the plant.

In May, the agency imposed a ban on products from Wockhardt’s Waluj plant, citing issues with the plant’s good manufacturing practices.

The warning letter, which also addresses issues with a re-inspection of the Waluj facility, says Wockhardt has routinely failed to accurately test for drug stability, follow written procedures and secure its system of computerized data, and that its quality unit may lack authority to enforce quality standards.

The FDA says Wockhardt laboratory personnel demonstrated that they can delete electronic raw data files from the local hard drive, and

(See Wockhardt, Page 12)
Idenix Sues to Keep Gilead’s Hep C Drug Off the Market

Following setbacks to its hepatitis C drug program, Idenix Pharmaceuticals is appealing to the courts to keep Gilead’s competing hepatitis C treatment off pharmacy shelves.

The FDA approved Gilead’s hepatitis C drug Sovaldi (sofosbuvir) was approved Dec. 6.

The small drugmaker filed a patent infringement suit in the U.S. District Court for the District of Massachusetts alleging that Gilead’s sofosbuvir infringes two U.S. patents co-owned by Idenix that cover methods of treating the hepatitis C virus (HCV) using 2’-methyl nucleosides.

Idenix also filed a patent infringement and interference lawsuit in the U.S. District Court for the District of Delaware claiming Gilead infringes a separate U.S. patent co-owned by Idenix that covers methods of treating the hepatitis C virus using 2’-methyl-2’-fluoro nucleosides.

Both lawsuits seek declarations that Gilead’s imminent distribution, importation, use, sale or offer to sell drugs containing sofosbuvir, a 2’-methyl nucleoside compound, infringes Idenix’s patents.

Based upon Idenix’s patents, the drugmaker appears to have a valid complaint to bring the cases into court, according to Andrew Williams, a partner at the intellectual property law firm McDonnell Boehnen Hulbert & Berghoff.

Where it will go from there is unclear, he said, adding that sometimes actions such as these are filed as negotiating tactics.

Unlike patent infringement suits filed under the Hatch-Waxman Act, Idenix’s suit will not delay the FDA review process or Gilead’s ability to market the drug, Williams added.

The FDA’s Antiviral Drugs Advisory Committee in October recommended the drug for approval, with some panelists relishing the “historic moment.”

Both Idenix and Gilead have been in a heated race with each other, Vertex Pharmaceuticals and other drugmakers to develop the first and most effective all-oral hepatitis C drug regimen. The hepatitis C market represents an estimated $20 billion in annual sales.

Idenix’s most promising candidate, IDX20963, experienced its first major setback in June, when the FDA asked the drugmaker to submit additional preclinical safety data, delaying the initiation of clinical trials for the candidate. Idenix is still in the process of performing the preclinical work for IDX20963 in response to the agency’s request, but a formal response has not been submitted to the FDA yet, Idenix spokeswoman Teri Dahlman told WDL Dec. 3.

The drugmaker had scrapped development programs for two other hepatitis C candidates after the agency last year placed clinical holds on them as a result of adverse event reports in a similar drug being developed by Bristol-Myers Squibb. — Melissa Winn

Implementing Risk-Based Verification and Validation

Switching to risk-based verification and validation is likely to save you money on projects, plus reduce liability and recalls. It’s a good business idea. And what’s more, the FDA is pushing you to do it. But like any basic change, there’s a learning curve. Are you ready?

This all-new management report from FDAnews is just the ticket for drug and device manufacturers ready to take the first step … and seeking a helping hand. It begins with the basics — understanding what risk-based V&V is — then shows how to start implementation in your operation. You’ll have to make the switch to risk-based V&V sooner or later. Why not start now? Order your copies of Implementing Risk-Based Verification and Validation.

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FDA Denies Small Pharma Company’s Request for GDUFA Facility Fee Waiver

The Generic Drug User Fee Amendments of 2012 do not allow for a waiver, reduction or postponement of finished dosage form (FDF) facility fees for small and/or foreign businesses, the FDA says in a letter denying a citizen petition submitted by Square Pharmaceuticals.

The agency says it also has no authority to change GDUFA’s statutory requirements. Congress would need to pass new legislation amending the FDF facility fee language and the president would have to sign it into law, CDER Director Janet Woodcock writes in reply to Square.

The drugmaker in July asked the FDA to revise GDUFA’s annual FDF facility fee requirement to allow for a “one-time FDF facility fee until the approval of the first ANDA” manufactured at the facility. The drugmaker also requested a waiver while the agency considered its petition.

Square Pharmaceuticals argued that GDUFA’s annual facility fee requirement is “burdensome and paralyzing to small size companies and/or foreign manufacturers.”

Instead, the drugmaker suggested a one-time fee could be charged at the same time the agency issues an approval letter or as a condition of approval for an ANDA. The facility would not be subject to any other fees under GDUFA until the product manufactured at the facility is commercialized, the petition said.

For new drugs approved under the Prescription Drug User Fee Act, the manufacturing facility fees are not charged unless the product is approved and commercialized by the NDA holder, the drugmaker reasoned.

The possibility of financial hardship for small to mid-size generic drug companies was discussed by the pharmaceutical industry and the FDA during GDUFA negotiations and all parties agreed that waivers and exemptions would not be included, the agency’s response letter says.

The decision was made “after considering the relatively low amount of expected individual fees” and the benefits to small and mid-size companies that will result from the speedier ANDA review times the fees allow for, Woodcock writes.

Priya Jambhekar of Chrai Associates, who filed the petition on behalf of Square, told WDL the company hopes some of these issues will be addressed when GDUFA comes up for review.


Phase III Failure Bruises Eli Lilly’s Blissful 2014 Outlook

Eli Lilly’s plans for strong sales growth in 2014 have been set back, with the drugmaker saying Thursday its promising depression treatment edivoxetine has failed in late-stage testing.

In three separate Phase III studies, the drug proved no more effective than placebo at improving symptoms of major depressive disorder in patients with treatment-resistant depression, the company said. Lilly will not pursue the drug as an add-on treatment for depression, it added.

Analysts had predicted the drug could rake in $300 million in sales by 2017.

With several key patents set to expire, the drugmaker is banking on its brimming pipeline to shore up sales by mid-2014. With edivoxetine out of the picture, Lilly now has 13 drug candidates in Phase III or in regulatory review.

Lilly expects to begin launching new products in 2014 and is “on track to return to revenue growth and margin expansion in 2015 and beyond,” Rice added.

Lilly will also investigate other potential indications for edivoxetine, a spokesman for the drugmaker told WDL. However, he said it was too soon to say what specific indications the company might pursue. — Melissa Winn
FDA Requests Nominations For Do-Not-Compound List

The FDA is building a list of difficult-to-manufacture drugs that compounders will not be allowed to make and is soliciting public suggestions for products to place on the list.

The agency also wants nominations for a list of bulk drug substances that may be used to compound drug products, the agency announced.

In addition, the FDA said it plans to withdraw a 1999 proposed rule that would have listed bulk drug substances acceptable for use in compounding. The rule was never finalized.

Nominations for the do-not-compound list should note the drug name and why it should be on the list. The FDA suggests valid reasons may include:

- The drug delivery system or formulation so sophisticated it can’t be reproduced;
- It is difficult to maintain or achieve a uniformly bioavailable dosage form; and
- A significant potential for error during compounding.

In selecting bulk substances for its approved list, the agency defined them as anything that becomes an active ingredient or finished dosage form of the drug. The term doesn’t include “intermediates used in the synthesis of such substances,” the agency said.

Proposed approved bulk drug substances should include:

- Whether the substance has been recognized by foreign pharmacopeias, and if information has been submitted to the U.S. Pharmacopeia for monograph development; and
- A bibliography of available safety and efficacy data.

The deadline for submitting nominations for the bulk drug list, docket no. FDA-2013-N-1524, and the do-not-compound list, docket no. FDA-2013-N-1523, is March 4.

To read the notice on the do-not-compound list, visit www.fdanews.com/ext/resources/files/12/12-3-13-DoNotCompoundList.pdf. The bulk drug substances notice is available at www.fdanews.com/ext/resources/files/12/12-3-13-BulkSubstancesList.pdf. The notice on withdrawing the 1999 rule can be read at www.fdanews.com/ext/resources/files/12/12-3-13-RuleWithdrawal.pdf. — Robert King

Compounding, from Page 1

If a facility registers before June 2, 2014, the agency does not intend to immediately enforce the requirement to report product information at the time of initial registration, as long as the facility submits its report within two months after the date of that initial registration, the registration guidance states.

Eventually, compounders will need to report to the agency using the existing structured product labeling format, but while the FDA improves its electronic reporting systems, companies should submit product information in an excel spreadsheet until the agency can improve its web interface, the reporting guidance states.

The agency’s new authorities were included in the Drug Quality and Security Act that was signed into law recently (WDL, Dec. 2).

The FDA last week also issued a third guidance on compounding pharmacies not classified as outsourcing facilities, explaining how the agency intends to enforce new restrictions on compounders’ advertising and promotions that the new law put in place.

Meanwhile, the FDA has also set its sights on Congress, seeking more money to support its new role overseeing compounding pharmacies, Commissioner Margaret Hamburg said during a conference call with reporters.

Comments on the reporting guidance, docket no. FDA-2013-N-1428, the registration guidance, docket no. FDA-2013-N-1429, and updated compounding guidance, docket no. FDA-2013-D-1444, are due by Feb. 2.

Baxter Recalls Nitroglycerin

Baxter has issued a recall for a single lot of the nitroglycerin 5 percent dextrose injection, a drug used for pre- and post-operative hypertension, congestive heart failure at the onset of heart attack and chest pain in certain patients.

The recall, which comes two months after Baxter recalled two dual luer lock caps, is due to particulates found in a single vial of the injectable drug. The affected lot was distributed to healthcare centers and distributors in Colombia, the U.S. and Saudi Arabia earlier this year.

No other lots or vials are affected and no adverse events have been reported, according to the drugmaker. Baxter spokeswoman Deborah Spak said the company is working closely with the FDA on managing the recall.

CMS Clarifies Reporting Requirements

The Centers for Medicare and Medicaid (CMS) Dec. 3 clarified a top concern of drugmakers: which format to use for submitting reports required under the Physician Payment Sunshine Act.

In an update to the agency’s Open Payments website, CMS clarified that drugmakers and group purchasing organizations (GPO) must submit payment reports in XML and CSV file formats.

Manufacturers and GPOs will have a 90-day window between Jan. 1 and March 31, 2014, to file 2013 information required under the law.

CMS cautions that along with the submissions, companies must also file attestations to the timeliness, accuracy and completeness of reported data.

The most recent submission with an attestation will be considered the final submission from a company. CMS will consider submissions without attestations as unreported.


Dyax Drug Gets Orphan Status

The FDA Dec. 2 granted Dyax orphan drug designation for its DX-2930 human monoclonal antibody that inhibits plasma kallikrein, reducing swelling, pain and inflammation characteristic of hereditary angioedema.

The small-volume, subcutaneous injection is currently being studied in a Phase I trial in the U.S., the results of which are expected in the first quarter of 2014. After that, says Dyax spokesperson Jennifer Robinson, the company plans to move on to Phase Ib and Phase II trials, contingent upon discussions with the FDA. Dyax would like to expand its patient base into the EU in Phase II and eventually move on to Phase III studies, though it does not yet have a set timeline.

Orphan drug designation, assigned to products that treat diseases affecting less than 200,000 U.S. patients, gifts Dyax with agency help in trial design, exemption from user fees and seven years of market exclusivity after approval.

MiMedx Agrees to FDA Oversight

After extensive discussions with the FDA, MiMedx has agreed to settle complaints of selling unlicensed products. It will submit BLAs for its tissue-based drugs; a move that may set precedent for other companies in the marketplace.

MiMedx said it still believes formal approval of its novel regenerative, human cellular and tissue-based products (HCT/Ps) isn’t necessary, but it will follow the FDA’s wishes.

The issue came to light earlier this year when the agency issued MiMedx an untitled letter for improperly marketing its HCT/Ps without FDA authorization.

MiMedx micronizes human tissues for use in drugs. The FDA ruled that the manufacturing process goes beyond the minimal manipulation that is allowed for simple human tissue products, and that the drugs fall under the FDA’s purview as regulated biologics.
Lawmakers Urge White House to Return Sequestered Fees to FDA

The White House Office of Management and Budget’s decision to sequester nearly $85 million of FDA user fees is wrong, and should be reversed immediately, lawmakers say.

In impounding the user fees under the 2011 Budget Control Act, OMB misinterpreted sequestration to apply to both congressionally appropriated funds and user fees, say Rep. Kevin Yoder (R-Kan.) and 73 other House members in a letter to OMB Director Sylvia Burwell.

In fact, OMB’s decision to sequester the private dollars flies in the face of the fundamental intent of the Budget Control Act, which instituted sequestration to reduce government spending of appropriated funds, the group says.

User fees, paid to the agency as part of an agreement negotiated between drugmakers and the FDA, have no bearing on spending of appropriated funds since they cannot be used to offset any expenses other than drug or device reviews. Sequestration of the user fees only exacerbates the FDA’s “severe budgetary constraints,” the lawmakers argue, urging the White House office to return the non-tax revenues to the agency.

The sequestration has resulted in $82 million in reduced user fee spending for the FDA, including $36.6 million in prescription drug and biologics user fees under the Prescription Drug User Fee Act, $15.25 million under the Generic Drug User Fee Amendments of 2012 and $2.85 million under the Medical Device User Fee Act programs, according to the lawmakers.

Congressional negotiators are under a Dec. 13 deadline to hammer out a new federal budget proposal for fiscal 2014 and fiscal 2015. As part of those negotiations, Yoder and other lawmakers are trying to shield FDA user fee revenue from any future across-the-board sequestration cuts.

— Melissa Winn

Budget, from Page 1

With few signs of progress, a growing chorus of House budget leaders is calling for a quick resolution. A group of 13 Republican lawmakers who chair House appropriations subcommittees want the committee to propose a deal on spending levels so debate can begin.

The lawmakers, led by Appropriations Chairman Rep. Hal Rogers (R-Ky.), say another government shutdown and a second sequester with “indiscriminate across the board” cuts is unacceptable. Failing to agree on a spending cap for fiscal year 2015 will also “guarantee another year of confusion,” the group said in a letter to the negotiators.

Meanwhile, another group of lawmakers is pleading with the budget negotiating committee to ensure that any deal protects FDA user fees from sequestration of other cuts.

The FDA lost $85 million in user fees in fiscal 2013 to the sequestration budget cuts. The funds are impounded and unavailable for use by the FDA or anyone else (WDL, Nov. 18).

Eshoo and a group of five senators introduced legislation in the House and Senate earlier this year to protect the fees from sequestration in fiscal 2014 (WDL, Aug. 12).

Industry has echoed the lawmakers’ call for protecting user fees. “Sequestration [of user fees] does not decrease the nation’s deficit, but only serves to exacerbate the severe budgetary constraints of a historically underfunded agency,” Matt Bennett, PhRMA senior vice president, told WDL.

To read the user fee letter, visit www.fdanews.com/ext/resources/files/11/11-26-13-UserFeeLetter.pdf. — Robert King

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<th>LEGISLATIVE ACTIONS</th>
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<td>Small Manufacturer Protection Act of 2013 (H.R. 3631)</td>
<td>Rep. Robert Hurt (R-Va.)</td>
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Regulators Expect to Reach EU Trial Compromise By Christmas

An agreement is expected to be reached on the Clinical Trial Regulation between EU lawmakers and the European Council by Christmas, and industry groups are asking to ensure the timelines for submissions are predictable and no longer than those already established in the current directive.

“The timelines set out by the Commission are achievable — we can look to Belgium and the United Kingdom as examples for best practice,” said Richard Bergström, director general of the European Federation of Pharmaceutical Industry Associations. “Where adjustments to national regulatory systems are required, these should be regarded as investment in the future.”

Amendments proposed in June would slightly prolong timelines in the European Commission’s original proposal, setting the time for approvals between 58 and 88 days. “However, given that under the current legal framework the maximum time for approval is 60 days and some member states are able to approve clinical trials in 28 days, the timelines should not be made any longer,” the European Organization for Research and Treatment of Cancer said in a position paper issued last month.

Besides a cap on approval timelines, the groups — which include the Association of Clinical Research Organizations, EuropaBio, Cancer Research UK and the Patients Network for Medical Research and Health — would like to see a more streamlined process for assessing applications to conduct EU trials and support for a more robust legislative mechanism to ensure compliance with timelines set forth in the legislation. The groups also want the Commission to ensure support for member states during implementation, to make certain timelines in the legislation are met. — Nick Otto

FDA API Shipment Refusal Prompts Lawsuit Impacting Border Control

The FDA’s unusual demand that an importer of active pharmaceutical ingredients (API) list the distributors that might sell finished product created with the API has sparked a lawsuit that could further complicate U.S. border control processes.

New York-based importer H&M USA sued the FDA in November after the agency detained an August shipment of 20,000 kilograms of acetaminophen because of no “end-use” documentation on where the API would end up.

H&M planned to sell the API shipment to Gemini Pharmaceuticals, which would in turn use it to contract manufacture OTC drugs for Rugby Laboratories. Both companies contacted the agency concerning the shipment, according to the lawsuit filed in the U.S. District Court for the Eastern District of New York.

However, the agency refused to admit the shipment in September because H&M didn’t submit a complete list of private label distributors that may sell the product. The agency was concerned the shipment would wind up in a warehouse, the lawsuit reads.

It isn’t unusual for the FDA to request end-use letters. However, the request for a list of private distributors and the concerns over inventory use are out of the ordinary, Dara Levy, an attorney with Hyman, Phelps & McNamara, told WDL Dec. 5.

“There is no statutory or regulatory prohibition to importing lawful product for warehousing and ultimate lawful sale,” she said.

H&M wants the court to release the shipment. If H&M loses its suit, it could be a warning to importers that they should prepare to more fully document uses of APIs, Levy said.

The agency has broad import powers, and can refuse any import based on the appearance of a violation as opposed to an actual one. The FDA said it doesn’t comment on pending litigation. — Robert King
Lawmakers Blast FDA’s Decision To Approve Opioid Zohydro ER

Several House members are calling on the FDA to strip Zohydro ER, Zogenix’s opioid pain-killer, of its approval until the company can instill an abuse-deterrent formulation of the product.

Zohydro ER (hydrocodone bitartrate extended-release capsules) was approved earlier this year as a single-entity hydrocodone Schedule II controlled substance with instructive labeling and indications for use, which the agency now requires for all extended release/long acting analgesics.

However, that labeling, which advises using the drug for severe pain in cases other than treatment for cancer, isn’t strong enough to stop abusers, reads a letter from eight House lawmakers to HHS Secretary Kathleen Sebelius and FDA Commissioner Margaret Hamburg.

Reps. Stephen Lynch (D-Mass.) and Hal Rogers (R-Ky.) are leading the charge against Zohydro. Both have been active in pushing legislation to mandate the FDA tighten the indications for approved controlled-release oxycodone HCl drugs (WDL, March 29).

Zogenix spokeswoman Julie Normart said the company is working on an abuse-deterrent formulation and hopes to have it on the market within three years.

The FDA is aware of the letter and Sebelius will respond to the lawmakers, agency spokeswoman Morgan Liscinsky told WDL.

The letter was also signed by Reps. Nick Rahall (D-W.Va.), William Keating (D-Mass.), Vern Buchanan (R-Fla.), John Tierney (D-Mass.), Michael Capuano (D-Mass.) and James McGovern (D-Mass.). — Robert King

Wockhardt, from Page 5

quality personnel use a single, shared user ID and password to access many stand-alone systems.

During the July inspection that prompted the warning letter, FDA investigators observed repeated instances in which the drugmaker performed “trial” sample high-performance liquid chromatography analyses before performing the “official” analysis for release and stability testing, the letter states. The practice is not recognized as a validated method, the FDA says.

Wockhardt quality control analysts also attempted to mask the practice of performing sample “trial” injections by labeling them as standard, the agency adds.

To clear the agency concerns, FDA wants Wockhardt to hire a third-party auditor to evaluate the drugmaker’s data integrity.

To ensure data is not inappropriately altered or deleted, the agency wants Wockhardt to identify:

- Any historical period(s) during which inaccurate data reporting occurred at its facilities;
- Current and former employees to be interviewed who might have relevant information regarding any inaccurate data reporting; and
- Specific managers in place when inaccurate data reporting occurred and determination of the extent of top and middle management involvement in, or awareness of, data manipulation.

Wockhardt did not return requests for comment as of press time.

Wockhardt, in an Oct. 2 response to a recent Form 483, indicated it would procure stability scheduler software to track and monitor stability plans and testing procedures. — Melissa Winn
Donald Deieso, CEO of WIRB-Copernicus, heads what he says is the oldest and largest independent institutional review board, founded in 1968. He is also on the board of directors of Sentrx, TractManager, Breckenridge Financial Services and IMDS.

**WDL:** What are some significant changes you’ve watched happen in the IRB arena over the past year and how do you think they will affect the research industry?

I think IRBs are being asked to take a more active role in assisting some of the clients in understanding some of the ethical issues associated with their work. At the WIRB-Copernicus Group we’ve responded to that need by creating a consulting division that sits very much apart from and separate from our IRB division. Our consultants are themselves in some cases former regulators, researchers, IRB professionals and bioethicists. They provide to sponsors a deeper understanding of the ethical issues associated with clinical trials. Sponsors are also becoming more discriminative, asking whether an IRB is accredited or not. We are great supporters of accreditation because it raises the bar for the entire industry.

**WDL:** Are there any regulatory issues you think are going to become more important in the coming years?

There is one glaring issue. To date there’s been some rather uneven enforcement of CFR Part 11. It’s important, as documents become increasingly more digitized, the requirement that those records be kept properly, be audited and that audit trails track any changes that have occurred to ensure transparency. In Europe they have the ISO standards, in this country it is Part 11 validation. I would imagine going forward we’re going to see more of those obligations by the FDA as they audit individual sites or ask sites to attest that they’re following those rules.

**WDL:** What one advice would you give to IRBs to help protect themselves?

If I had a single recommendation, it would be to have a robust and substantial quality assurance program and team. For many of the smaller IRBs this becomes quite costly to manage. As with anything else involving human beings, where error is possible, your quality program and the quality professionals who are constantly monitoring your activities are your safeguard. Quality is one of those costs you make behind the scenes, you make investments in it and it’s protecting you. It’s like a life insurance policy.

**WDL:** How do you see the industry changing in the coming years?

One prediction is there may be fewer of the very large blockbuster trials. They will give way to smaller but much more focused and more complex trials. We employ on a full-time basis about 18 physicians and 16 to 18 regulatory attorneys, and these are not individuals who are on the IRBs. These are individuals who are on our staff and are constantly looking at advances in the science and the art so we can be more helpful to our clients in the proper construct of a clinical trial. I think that’s necessary going forward because it’s getting more complex. We’re not seeing large hypertensive drug trials. I’m predicting that there will be a continued consolidation in the IRB industry. There are at least a couple hundred small IRBs all over the country doing a little bit of review here and a little bit of review there. A lot of these small companies will be absorbed into the larger IRBs. You are also going to see sponsors and regulators together look at the IRB’s role and begin to give it more oversight.
GPhA Asks the FDA to Extend Comment Period on Labeling Rule

The FDA’s proposed new labeling requirements for generics pose such a challenge to industry that GPhA has asked the FDA for an additional two months to comment on the proposed rule.

GPhA says more time is needed to analyze and provide commentary on the legal and commercial implications of the rule change, which would allow generics makers to change labeling without FDA approval in response to safety concerns.

Current rules allow generic drugmakers to update labeling only as a means of conforming with changes made to the brand-referenced drug’s label. This has largely shielded generic makers from injury suits.

The proposed rule nullifies a 2011 Supreme Court decision in the case of Pliva v. Mensing, in which the court rejected the notion that generic companies have an obligation to request label changes after new adverse events were found, Daniel Kracov, a partner at Arnold & Porter, says.

If the rule is finalized, generic drugmakers will need specific evidence to fend off lawsuits that claim the drugmaker failed to warn about serious side effects, because the courts could find them liable in the same way they have found brand drugmakers liable for years, Kracov told WDL.

The proposed rule would present a host of business issues, as well, he said, noting that most generic drugmakers don’t currently have systems in place to analyze adverse event reports for signals that would prompt a labeling change.

Shortly after the proposed rule was issued last month, GPhA questioned whether the agency has the authority to issue the rule in the wake of the court’s decision (WDL, Nov. 11). The group also said it is concerned that multiple generic drugmakers could file conflicting safety information for the same generic product, leading to “unnecessary confusion and uncertainty for prescribers and patients.” — Melissa Winn

TPP, from Page 3

the TPP talks got under way to urge that 12 years of exclusivity be obtained (WDL, Sept. 16, 2011). That effort has continued, with members of both houses of Congress and governors from 11 states repeatedly expressing support for the extension of the 12-year standard to the TPP, Grayson added.

Industry stakeholders such as GPhA, the Japan Generic Medicines Association and the Canadian Generic Pharmaceutical Association, have argued that biopharmaceuticals should not be protected at all by an exclusivity period. Sales data show that innovator companies retain most of their market share even after the expiration of the patents, making a regulatory exclusivity period unnecessary, the groups argue.

The administration, however, has sided with pharma. Following a full day of discussions Nov. 29, the Office of the U.S. Trade Representative said biologic drugs need data protection to offer incentive to companies willing to invest the enormous amounts of time and money to develop them. — Melissa Winn
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