Generic Drugmakers to Inherit Safety Labeling Update Powers Under FDA Rule

The FDA is proposing to give generic drugmakers the power to revise product labeling in response to safety issues prior to agency approval — a power that brand drugmakers already have.

Under a new proposed rule, generic manufacturers would make the labeling change by filing a “changes being effected” supplement (CBE-0) for their drugs. The CBE-0 should contain:

- The application number of the drug product(s) involved;
- A description of the labeling change proposed in the supplement;
- The basis for the change, such as data from adverse event reports or published literature;
- A copy of the product labeling proposed in the CBE-0 supplement; and

(See Labeling, Page 4)

Senate Passes Pharmaceutical Track-and-Trace Legislation

Drugmakers have 13 months to revamp how they track drugs after the Senate voted Nov. 18 to send to President Barack Obama’s desk a measure that would establish a nationwide track-and-trace requirement for prescription drugs.

H.R. 3204, the Drug Quality and Security Act, was approved by a voice vote without amendments following House passage in late September.

Once signed into law, H.R. 3204 will immediately preempt all state laws concerning track-and-trace, including California’s strict e-Pedigree measure set to go into effect in 2015.

GPhA President and CEO Ralph Neas applauded the bill’s passage, saying a consistent national standard for tracking prescription drugs will help regulators limit risks posed by counterfeit or adulterated products.

(See Track-and-Trace, Page 6)
SCOTUS Deals Teva Crucial Blow In Drawn-Out Copaxone Patent Battle

The Supreme Court Nov. 13 dealt generic giant Teva a major blow as it denied the company’s request to stay a lower court’s ruling that will allow generic versions of the drugmaker’s blockbuster brand drug Copaxone to hit pharmacy shelves in May.

Without explanation, Chief Justice John Roberts rejected Teva’s plea to stay the ruling while the company prepares a petition for Supreme Court review.

Teva will ask the high court to review a decision handed down in July by the U.S. Court of Appeals for the Federal Circuit. The appellate court reversed a decision by the U.S. District Court for the Southern District of New York and declared several Copaxone (glatiramer acetate injection) related patents expiring in May 2014 and one patent expiring in September 2015 to be invalid. The appellate court specifically ruled that asserted claims of these patents are invalid for being indefinite, Teva said at the time (Generic Line, July 31).

Any Supreme Court review of the case likely won’t happen until its next session, which begins in October 2014 and gives generic copycats of the multiple sclerosis drug at least six months worth of sales.

That kind of hit to Teva could be crucial, given that the drug earned the drugmaker nearly $4 billion last year and accounts for 50 percent of its profits.

Mylan is readying to launch its generic version of Copaxone on May 25, 2014.

Teva has fought a long and hard losing battle to stave off generics of its leading innovative drug.

The Israeli drugmaker filed four citizen petitions asking the FDA to impose specific conditions on approved generic versions of Copaxone (Generic Line, Jan. 2). The agency denied them all.

The drugmaker also has pending lawsuits over Copaxone in the U.S. and overseas, most of which concern patent challenges mounted by Mylan (Generic Line, Sept. 14, 2011). — Melissa Winn

EU Pharmacovigilance Notification Requirements Are Now In Effect

For the first time brand and generic drugmakers are required to notify the EMA and individual country regulators when they withdraw a drug from the market anywhere in the EU, and the reasons why, to comply with the EU’s newly amended pharmacovigilance law.

As of Oct. 28, marketing-authorization holders must satisfy the new reporting requirements that apply to the suspension, withdrawal, request to withdraw or intention to not renew authorization of a drug, the EMA says. Notifications apply in the following instances:

- When a drug is found to be harmful;
- When the drug lacks therapeutic efficacy;
- When a drug’s benefit-risk balance is not favorable;
- When the qualitative and quantitative composition of a drug are not as declared; or
- When new manufacturing or inspection issues have been identified.


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<th>New Paragraph IV Patent Certifications (As of Nov. 4, 2013)</th>
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Generic drugmakers file ANDAs with Paragraph IV certifications on drugs where patent coverage still exists and they intend to market generics before the patent expires if approved.
Generic Drugmakers Should Prepare For FDA Inspection Focus on Metrics

The FDA plans to shift its focus during facility inspections away from examining documentation, such as standard operating procedures, and place more emphasis on a facility’s operational metrics.

“We really want to know more about the results,” not the design, of a facility’s quality system, CDER Director Janet Woodcock said Nov. 4.

The agency plans to require brand and generic drug manufacturers to submit data about specific quality metrics within a year or two; it is still deciding what metrics to require, although officials have floated metrics such as batch failure rates or complaint data.

Woodcock, speaking at the 2013 annual meeting of the International Society for Pharmaceutical Engineering (ISPE) in Washington, D.C., said the FDA wants to find metrics that would be appropriate and simple. ISPE is currently conducting a project to solicit feedback from industry on objective and useful metrics. The goal is to develop a white paper that is acceptable to industry and regulators that defines the best metrics for use in a risk-based inspection program (Generic Line, Sept. 25).

Woodcock said that many companies already belong to quality organizations such as Six Sigma, and use measures that assess how well they are doing. However, some companies have complained that such measures and metrics are “internal tools” that would be too burdensome for them to report and cause confusion in the marketplace (Generic Line, May 8).

The push for quality metrics is tied to legislative mandates in the FDA Safety and Innovation Act to conduct more risk-based inspections. The FDA doesn’t plan to publish quality scores for individual companies, said Woodcock. The goal is to publish “the state of quality of manufacturing in the pharmaceutical industry,” she said.

By publishing an overview of how the industry is doing as a whole, “individual companies can benchmark themselves against that,” Woodcock said. She added that the agency is willing to consider a reward for companies with a good quality record. One such incentive could be more regulatory freedom to operate, Woodcock said, but she declined to elaborate on that concept.

(See Metrics, Page 8)

Judge Says Biosimilars Law Prohibits Premature Patent Suit

A California judge has ruled that Sandoz must file an application with the FDA for approval of a biosimilar referencing Amgen’s biologic arthritis drug Enbrel before it can challenge the brand drug’s patents.

The ruling in the closely-watched case could discourage biosimilar makers from making preemptive strikes against innovative products, a common tactic generic drug manufacturers employ against branded drugs.

Sandoz is currently conducting clinical trials on its own etanercept product and plans to file an application to license it as a biosimilar upon completion of those trials, the drugmaker told the U.S. District Court for the Northern District of California.

Sandoz had argued that federal law provides for declaratory judgment actions to be filed by either party once the biosimilar manufacturer gives the reference drug sponsor “notice of commercial marketing,” which Sandoz has done.

The court was not persuaded, noting that a notice of commercial marketing is only required by law for licensed products.

Sandoz cannot, as a matter of law, have provided a “notice of commercial marketing” because its etanercept product is not licensed under the Biologics Price Competition and Innovation Act of 2009, Chesney wrote in an order granting Amgen’s motion to dismiss the case. — Melissa Winn
Labeling, from Page 1

- Confirmation that the brand drugmaker was notified of the CBE-0 supplement.

Under current law, a branded drugmaker usually implements labeling changes around the time it submits the CBE-0 supplement. The FDA will review the supplement and then either approve it or send a letter to the drugmaker with proposed changes. Currently, generic makers must wait for agency approval before implementing the change.

The agency plans to post CBE-0s for NDA, ANDA and BLA products on a new web page. Because of this new feature, the agency wants all CBE-0s to be submitted in a structured product labeling format that can be posted online, the FDA said.

The proposed rule touches on issues raised in a 2011 Supreme Court decision in the case of Pliva v. Mensing. In that case, the court rejected the notion that generic companies have an obligation to request label changes after new adverse events were found (Generic Line, July 20, 2011).

“The federal statutes and regulations that apply to brand-name drug manufacturers differ, by Congress’ design, from those applicable to generic-drug manufacturers,” Justice Clarence Thomas wrote for the majority. The FDA and Congress may change the laws and regulations if they desire, he adds.

GPhA Nov. 8 questioned if the agency has the authority to issue the rule in the wake of the court’s decision.

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.”

GPhA said it is reviewing the proposed rule, evaluating it “both for any elements that could impact patient safety, and for our member company business practices.”

The proposed rule was published in the Federal Register Nov. 13. The public has until Jan. 12 to comment. The proposed rule is available at www.fdanews.com/ext/files/11-08-13-ProposedRule.pdf.

— Robert King

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EMA Offers Generic Makers Roadmap to Bioequivalency

The European Medicines Agency (EMA) has provided generic drugmakers its first roadmap to meeting standardized EU bioequivalence requirements.

The agency Nov. 15 issued individual guidances detailing how bioequivalence studies will be conducted for 16 active substances — the first in a planned wave of product-specific guidance.

The guidance aims to help drugmakers design studies that meet EU regulators’ expectations and promote consistency in the EMA’s assessments of applications seeking authorization of generics.

For each drug, the agency provides guidance on: a biopharmaceutical classification system; the type of bioequivalence study design; the component (parent drug or metabolite) to be evaluated; and bioequivalence assessments. The 16 active substances covered are:

- Genentech’s capecitabine (Xeloda), oseltamivir (Tamiflu) and erlotinib (Tarceva);
- Pfizer’s sirolimus (Rapamune) and voriconazole (Vfend);
- Orphan Europe’s carglumic acid (Carbaglu);
- Bristol-Myers Squibb’s dasatinib (Sprycel);
- Gilead’s emtricitabine/tenofovir disoproxil (Truvada);
- Novartis’ imatinib (Gleevec);
- Forest Laboratories’ memantine (Namenda);
- Actelion’s miglustat (Zavesca);
- Schering-Plough’s posaconazole (Noxafil);
- Novo Nordisk’s repaglinide (Prandin);
- Onyx’s sorafenib (Nexavar);
- Eli Lilly’s tadalafil (Cialis); and
- Sanofi’s telithromycin (Ketek).

The FDA has published draft or final bioequivalence recommendations for all 16 active ingredients.

Pharmacokinetics Q&A Update

The EMA earlier this month also updated its Q&A guidance on pharmacokinetics to highlight the importance of in vivo bioequivalence studies. “Bioequivalence is in principle demonstrated by means of in vivo bioavailability studies,” the agency said. However, “in vivo studies can be waived if the product fulfills the requirements defined in surrogate tests,” the update clarifies.

The 16 individual guidances can be found on the EMA’s website. To view the updated Q&A guidelines, visit www.fdanews.com/ext/files/11-18-13-EMAguide.pdf. All comments are due by Feb. 15, 2014, and should be sent to pkwpsecretariat@ema.europa.eu. — Nick Otto

More Pharma Patent Agreements To Be Reviewed Under FTC Rule

Drugmakers will soon have to seek Federal Trade Commission antitrust review for all proposed licensing agreements for “exclusive” patent rights.

The newly amended rule, published Nov. 15, will not apply to deals between brand and generic drugmakers for the market of authorized generics, as those are typically “non-exclusive,” Peter Kaplan, an FTC spokesperson, told Generic Line.

But any deal between generic makers and brand makers that includes the license of exclusive rights will need to be reviewed.

The rule expands the meaning of “exclusive patent rights” to adapt to increasingly complicated licensing deals in which drug companies transfer most, but not all, of the patent rights to “make, use, and sell” under an exclusive license.

Under current rules, companies could retain limited rights to a product and avoid FTC scrutiny, but still effectively transfer the exclusive rights to a product.

Under the new rules, in determining reportability, the parties should analyze what the licensor is transferring to the licensee and determine “whether the license conveys the exclusive right to commercially use the patent or part of a patent,” according to the rule.

After the companies report a proposed deal, the FTC and Department of Justice will conduct a preliminary review to determine whether the agreement raises any antitrust concerns that

(See FTC, Page 6)
The legislation sets a number of important deadlines for manufacturers.

By Jan. 1, 2015, all finished-dose forms of prescription drugs must include a lot-level transaction history that documents each step a product takes from manufacturer to final sale. Manufacturers face the same deadline for establishing a system to quarantine, investigate and validate via the history record a product suspected of being counterfeit, adulterated or stolen.

The bill also states that four years after enactment drugmakers must affix product identifiers to each package and case of a product that includes a numerical identifier, lot number and expiration date. When a manufacturer receives a returned product that it intends to redistribute, that manufacturer must verify the product identifier on each package beginning four years after enactment.

Ten years after enactment, manufacturers must develop an electronic traceability system that identifies products down to the sales-unit level.

The bill also directs HHS to seek public and industry input and issue guidance that:

- Defines the circumstances in which a manufacturer can infer that drugs in a large container are what they purport to be. HHS must hold a public meeting on the issue and then issue a guidance 18 months after that meeting;
- Explains how drugmakers and other supply chain stakeholders can get a waiver from any of the law’s requirements. The guidance is to be issued no later than two years from the date of enactment;
- Helps drugmakers establish mechanisms to identify a suspect product and what to do after it is identified as such. This guidance must be published no later than 180 days after enactment; and
- Provides detail on how to grandfather products that were already distributed in the supply chain when the bill became effective.

This guidance is to be issued no later than two years from the date of enactment.

The agency is also tasked with creating standards for the interoperable and secure electronic exchange of data along the supply chain. The standards must be available 18 months after a public meeting on the electronic system.

HHS must hold at least five public meetings in all to solicit feedback on how to implement the law, and at least one pilot project that evaluates unit-level traceability and the use of the product identifier.

Read the bill at www.fdanews.com/ext/files/11-12-13-HouseBill.pdf. — Robert King

FTC, from Page 5

warrant closer examination. During the preliminary review, the parties must wait 30 days before closing their deals, Kaplan said. The waiting period is halved to 15 days in the case of a cash tender or bankruptcy transaction.

Based on what the agency finds, it will either:

- Terminate the waiting period and allow the parties to consummate their transaction (often referred to as an “early termination”);
- Let the waiting period expire, which allows the parties to consummate the transaction; or
- If the initial review has raised competition issues, the review may be extended and the parties may be asked to turn over more information (referred to as a “second request”).

Most deals reviewed by the FTC and DOJ are allowed to proceed after the first preliminary review, according to the FTC.

PhRMA opposes the rule, arguing that the new requirements unfairly single out drugmakers and will heap significant financial and reporting burdens on them. The FTC disagrees, saying the “uniqueness” of pharma licenses results in exclusive licensing deals not seen in any other industry.

The amended rule Premerger Notification; Reporting and Waiting Period Requirements can be read at www.fdanews.com/ext/files/11-07-13-FTC.pdf. — Melissa Winn
FDA May Extend Comment Deadlines

The FDA may extend comment deadlines for certain drug-related regulations and guidance because the system through which online comments are submitted, Regulations.gov, was down for several days earlier this month.

Dockets that were affected by the outages and that may see comment period extensions include the agency’s new proposed rule on preventing and mitigating drug shortages, issued a few days ahead of the downtime.

The agency has yet to determine exactly which dockets were affected by the downtime. But the FDA's centers are reviewing pending dockets to decide which deadlines to extend, CDER spokesman Kristofer Baumgartner told Generic Line.

“The website’s reliability issues have caused delays in getting website content posted and general website updates. We have corrected those issues and will resume posting accurate and timely information,” he added.

FDA Approves Generic Aciphex

The FDA has approved the first generic versions of Aciphex (rabeprazole sodium) delayed-release tablets, used to treat gastroesophageal reflux disease (GERD) in adults and adolescents ages 12 and up.

Dr. Reddy’s Laboratories, Kremers Urban Pharmaceuticals, Lupin Pharmaceuticals, Mylan, Teva and Torrent Pharmaceuticals have all received FDA approval to market generic rabeprazole.

Rabeprazole is in a class of medications called proton-pump inhibitors. The medication works by decreasing the amount of acid made in the stomach, treating the symptoms of GERD such as heartburn, regurgitation of acid and nausea.

Hospira Expects 2014 Rebound

After a costly revamp of production facilities due to quality control issues, Hospira expects to near the “top end” of production capability in 2014, its CEO said Nov. 6.

Company-wide remediation efforts have cost the generic drugmaker $458 million since it was first warned by the FDA in 2010 for particulate contamination problems. Since then, it has struggled with shortages as it labored to maintain scaled-back production under the scrutiny of third-party auditors.

In 2013, the company is posting quarterly revenue increases again, and a recent inspection of Hospira’s Lake Forest, Ill., facility resulted in no Form 483, Hospira CEO Michael Ball said on a conference call.

Production at Rocky Mount has been steadily ramping up and revisions to its quality system to improve its investigations capacity are now at a point where sustainable compliance can be assured in the eyes of third-party auditors, he added.

Some less significant manufacturing deficiencies continue to trouble the drugmaker, however. In August, it received a three-observation Form 483 at its Kansas plant. FDA investigators criticized the McPherson, Kan., facility for an inadequate response to finding glass particles in sterile lyophilized drugs. During the inspection of the facility, the agency found that inspections into the particles were conducted long after discovery.

For example, Hospira received a customer complaint in April and received a sample on May 20 but didn’t complete the investigation until June 24. Investigators also found that Hospira failed to classify glass particulates as a “critical defect” even though there is a potential for causing adverse health consequences, the form reads.

Ball said on the conference call that the company responded with a corrective action plan and does not expect a warning letter.

Novo Nordisk Counsel Joins Firm

Former Novo Nordisk general counsel James Shehan has joined Hyman, Phelps & McNamara. Shehan’s work at the firm will focus on the handling of federal enforcement actions; corporate compliance and good manufacturing practices; Hatch-Waxman and advertising litigation; private and public transaction due diligence; drug development; and biosimilars.
EFPIA Says Drugmakers Should Establish Drug Shortage Task Forces

In the wake of record-breaking numbers of drug shortages, particularly generic injectables, the European Federation of Pharmaceutical Industries and Associations (EFPIA) is advising drugmakers to establish a drug shortage task force.

The task force should be comprised of upper management and quality personnel specifically focused on preventing shortages, according to new good practice guidelines developed by EFPIA.

The task force, which should also include outside representatives from the company’s supply chain partners, should be charged with maintaining quality and inventory processes to ensure patients have access to medicines, the 40-member trade group says.

The guideline points to four particular risk areas in the manufacturing process that the task force should closely monitor: market dynamics risk, upstream supply chain risk, distribution risk and manufacturing system risks.

Each area should have a performance indicator or indicators assigned to it, the group says. For example, when identifying market risks, performance indicators would be established to measure estimated drug demand and actual demand. To assess a company’s supply chain, the task force should establish indicators for the number of batches postponed, the estimated coverage of product supply and the actual coverage of supply.

Carefully monitoring the indicators will allow companies to know when they are nearing a situation that could create a shortage, says EFPIA.

EFPIA also stresses that companies should comply with EU good manufacturing practices reporting requirements. If a product has been manufactured incorrectly, has deteriorated over time or become the subject of a counterfeit campaign, the company should inform all concerned competent authorities, the guidelines note.

The communication component is also at the heart of a new FDA proposed rule intended to mitigate drug shortages. Certain drug and biologic manufacturers must notify the agency at least six months before they believe a product may be permanently discontinued or experience an interruption in manufacturing (Generic Line, Nov. 6).

View the guidelines at www.fdanews.com/ext/files/11-12-13-EFPIA.pdf. — Nick Otto

Metrics, from Page 3

The upside for drugmakers under the risk-based inspection regime is that better-performing companies would face fewer inspections.

The idea of financial incentives for companies that make manufacturing and product quality improvements was floated in a strategic plan to combat drug shortages unveiled last spring. The plan didn’t elaborate on what the incentives could be, and noted that the agency has a limited ability to offer such rewards. — Robert King
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