FDA to Tackle Industry Concerns With First Biosimilars Meeting

The FDA may end its silence on how an approval pathway for biosimilars will work once it gets feedback at its first public meeting on the topic next month.

The meeting, which will be held Nov. 2 and 3, will address several of industry’s most pressing questions since the creation of the pathway earlier this year. Issues slated for discussion include what it will take for a product to be deemed “interchangeable” and how a biosimilars user fee program should be structured, the FDA says in a Federal Register notice published this month.

The agency plans to ask stakeholders at the meeting what scientific and technical factors it should consider when determining whether a proposed biosimilar is “highly similar” to its brand counterpart.

(See Biosimilars, Page 2)

Apotex Revives Cozaar, Hyzaar Suit With Appeal to Supreme Court

Apotex has asked the Supreme Court to hear a case that could have a lasting impact on how initial marketing exclusivity is awarded to generic-drug manufacturers.

Apotex’s petition for a writ of certiorari involves a dispute over the FDA’s awarding, earlier this year, 180 days of marketing exclusivity to Teva as the first company to challenge a patent on Merck’s hypertension drugs Cozaar (losartan potassium) and Hyzaar (hydrochlorothiazide/losartan potassium).

Apotex had argued that Teva should not get the exclusivity because Merck had delisted its patent on the drugs from the FDA’s Orange Book, which under the Medicare Prescription Drug, Improvement and Modernization Act (MMA) is a valid reason for canceling a generic-drug maker’s marketing exclusivity.

(See Apotex, Page 4)
Biosimilars, from Page 1

This will include factors the FDA should consider when deciding the extent, if any, of clinical trials and the range of structural differences between a proposed biosimilar and its reference product that would be acceptable.

The interchangeable label, which would allow pharmacists to substitute a biosimilar for its brand counterpart without a doctor’s consent, also will be addressed, with the agency asking stakeholders what should be required for a drug to receive an interchangeability designation and how the risks associated with it should be evaluated.

In addition, the agency will tackle one of the most controversial issues of the biosimilars law — the 12-year exclusivity period granted to holders of approved BLAs.

Fear of Evergreening

A major question among stakeholders, especially generic-drug makers, has been how that exclusivity provision would be interpreted by the FDA and whether that interpretation could lead to so-called “evergreening” of brand biologics — where even a small change in the manufacturing process for an already-marketed biologic could provide another 12 years of exclusivity (Generic Line, May 26).

The FDA acknowledges the issue in the notice, saying it wants guidance on what factors it should consider before granting an additional 12-year period of exclusivity.

With a mandate to submit biosimilar user fee recommendations to Congress by January 2012, the FDA appears set to use the Prescription Drug User Fee Act as a model for the fees, but it is asking what changes it should make and whether the fees also should be used to monitor postmarket safety.

While the FDA notes that drugmakers do not need to wait for guidance before submitting biosimilar applications, it does intend to issue such documents and asks stakeholders which areas should be a priority during the early period of implementation.

— David Belian

BMS Hits Teva With Patent Suit Over Hepatitis B Drug Baraclude

Bristol-Myers Squibb (BMS) has filed a patent infringement lawsuit against Teva Pharmaceutical Industries after the generic-drug maker asked the FDA for approval to market a generic version of BMS’ hepatitis B drug Baraclude.

In the lawsuit, which was filed last month in the U.S. District Court for the District of Delaware, BMS says that Teva’s application is an act of infringement against its ’244 patent on the drug.

Teva disputed that notion in its Paragraph IV certification included with the ANDA, saying that the ’244 patent is invalid and would not be infringed by the company’s manufacture or sale of generic Baraclude (entecavir) 0.5- and 1-mg tablets.

BMS, however, is asking the Delaware court to issue an injunction preventing Teva from manufacturing or selling the drug until the ’244 patent expires in February 2015.

The company is also seeking reimbursement for its attorney’s fees and expenses involved with the suit, as well as additional monetary relief.

Baraclude was approved by the FDA in 2005 for the treatment of chronic hepatitis B infection in adults with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases or histologically active disease.

A black box warning was added to the drug’s label two years later, stating that Baraclude is not recommended for patients who are co-infected with HIV and hepatitis B and are not receiving highly active antiretroviral therapy due to the potential for the development of HIV resistance.

The drug was BMS’ third-best selling virology treatment in 2009, bringing in about $734 million in worldwide sales. — David Belian
Teva Hits Snag With Application For Biosimilar of Neupogen

Teva has received a complete response letter from the FDA for its BLA for the cancer treatment Neutroval, a biosimilar of Amgen’s Neupogen.

The agency requested several items from Teva but did not require additional clinical trials of the drug, the company said last month. Teva is now working with the FDA to determine the appropriate next steps for its application.

Teva is seeking approval for Neutroval (granulocyte colony-stimulating factor) for the reduction in the duration of severe neutropenia and the incidence of febrile neutropenia in patients treated with established myelosuppressive chemotherapy for cancer.

Amgen May Resist

While the drug has already been approved in Europe, if Teva’s BLA is eventually approved by the FDA, the company could face resistance from Amgen, which has the exclusive right to market Neupogen (filgrastim) until December 2013.

“We stress that intellectual property trumps all in this case and remain confident that Amgen’s patent estate will preclude this threat [from Neutroval] into late 2013,” Christopher Raymond, an analyst with Baird, said in a note.

Outside of the U.S., Neupogen biosimilars have gained a market share of only 4 percent, despite being on the market for about two years, Raymond added.

U.S. sales of Neupogen reached $901 million last year.

Among those marketing a generic version of the drug in Europe is Sandoz. The EU approved its human growth hormone Omnitrope (somatropin) in April 2006.

The product is similar to Pfizer’s Genotropin (somatropin recombinant) and is indicated for treating growth hormone deficiency.

The company also has EU approval for Binocrit (epoetin alpha), which is similar to Janssen Pharmaceutical’s erythropoiesis-stimulating agent Eprex. Binocrit was approved in the EU in August 2007 and marketed the same year.

For Teva, the world’s largest generic-drug maker, Neutroval is only the beginning of the company’s plans to expand into biosimilars.

The company is looking to become a global leader in the field, Teva’s CEO Shlomo Yanai said in announcing the Neutroval BLA filing last year, adding that $60 billion worth of biologic products will lose patent protection from 2013 to 2015.

Annual Investment

Teva planned to spend an estimated $100 million annually on follow-on biologics (FOB) R&D in 2009 and 2010, according to Yanai, who said that he sees few generic competitors entering the FOB arena, and many companies might have to seek partners on biosimilars because of the risks and high costs associated with their development.

Since that time, the company has launched a clinical trial for a biosimilar of Roche Genentech and Biogen Idec’s autoimmune disease drug Rituxan (rituximab) (Generic Line, June 9).

The trial, for which the company started enrollment last month in Germany and Hungary, will compare Rituxan, sold as MabThera in Europe, with Teva’s biosimilar, TL011, in about 60 subjects with severe, active rheumatoid arthritis. It is expected to be completed by mid-2011, according to clinicaltrials.gov.

Unlike some of its competitors, however, Teva has chosen not to wait for the FDA to develop the congressionally mandated approval pathway for biosimilars and has filed its applications as BLAs, requiring the drugmaker to conduct clinical trials.

The FDA is still working on how to implement the approval pathway and is set to hold a two-day public meeting next month.

— David Belian
Teva challenged that interpretation of the MMA in federal court, however, and the U.S. Court of Appeals for the District of Columbia Circuit ruled in the company’s favor (Generic Line, March 17).

Prior to that ruling the FDA had been allowing brand manufacturers to delist any challenged patents, stripping generic makers of the 180-day period of exclusivity for being the first to file, Chad Landmon, patent lawyer and partner with Axinn, Veltrop & Harkrider, told Generic Line at the time.

Following the ruling though, it was also discovered that Merck’s patent on the drugs had expired, another reason the MMA gives as a means for canceling generic exclusivity.

FDA Disagreed

While the FDA said it disagreed with the appellate court’s ruling, it nonetheless approved Teva’s exclusivity, saying the court’s interpretation of the MMA gave it no choice (Generic Line, March 31).

In the FDA opinion — written by Gary Buehler, the director of the Office of Generic Drugs — the FDA says that were it to consider the case as a “clean slate,” it would rule that patent expiration for any reason would also result in the forfeiture of a generic-drug maker’s exclusivity period.

According to the court’s decision, however, any unilateral action by a brand-drug maker, such as delisting a patent or letting it expire, cannot be used as a means for canceling a generic-drug maker’s exclusivity, the FDA said.

Apotex’s appeal to the Supreme Court is no longer a challenge to Teva’s exclusivity, which expired earlier this month. Instead, the company says, how exclusivity is awarded in all future cases is at stake.

“If left undisturbed, the decision will benefit brand-name manufacturers, who want nothing more than to see a first applicant win exclusivity and thereby delay full-scale competition with multiple generic manufacturers,” Apotex says. “It will also richly reward the generic manufacturer who wins a race to file a Paragraph IV certification but is unable promptly to bring the generic drug to market.”

For Merck, the appellate court ruling and subsequent FDA decision were favorable for the company, because the original opinion would have allowed not only Teva but also all generic manufacturers to sell their approved losartan potassium products beginning earlier this year.

Annual U.S. sales for Hyzaar and Cozaar are about $1.5 billion, Teva says.

The petition is listed under Apotex, Inc., v. Kathleen Sebelius, in her Official Capacity as Secretary of Health and Human Services, et. al. — David Belian

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Endo Buys Qualitest Pharmaceuticals In Move to Build Up Generics

Endo Pharmaceuticals has moved to strengthen its generic drug business, agreeing to acquire Qualitest Pharmaceuticals for $1.2 billion.

The deal, announced by the companies last month, will give Endo control of the sixth-biggest generic-drug maker in the U.S., as measured by prescriptions filled.

The combined company will have an extensive pipeline of ANDAs, with 46 under active review by the FDA in treatment areas including pain, neurology and oncology among others, Endo says. An additional 24 ANDAs are under development in multiple therapeutic areas.

“Qualitest brings a similar approach to how we target the generic market,” David Holveck, Endo’s president and CEO said in a conference call last month. “Our existing generics business focuses on difficult-to-formulate products. Qualitest also targets markets with high barriers to entry including controlled substances and liquids.”

New Revenue System

In addition, the deal will provide Endo with four manufacturing and distribution facilities and allow the company to decrease its dependence on the pain treatment Lidoderm (lidocaine patch), which accounted for about 50 percent of the company’s revenue last year, Alan Levin, Endo’s chief financial officer, said on the call.

That dependence was a fear among analysts covering the company, who had noted that Endo is also set to lose exclusivity on its pain drug Opana ER (oxymorphone HCl) in 2012 (Generic Line, June 23).

“They need to buy something and buy something big, something tangible and soon,” James Molloy, an analyst with Caris & Company, told Generic Line earlier this year.

Endo anticipates that the combined company will launch 25 products in the next two years and will have more than $500 million in revenues from its generics business in 2011.

For Qualitest, the deal will expand the profile of the privately held company and mark a turning point from manufacturing issues that led to the company receiving a warning letter and 483 observations.

The company’s two most recent inspections, at its facilities in Charlotte, N.C. and Huntsville, Ala., were much more positive, turning up no reports from the FDA, Marvin Samson, Qualitest’s chairman and CEO, said last month.

— David Belian

Endo, Watson Reach Settlement In Opana ER Patent Lawsuit

Endo Pharmaceuticals has reached a settlement with Watson Laboratories in a patent-infringement case over the pain drug Opana ER.

The settlement, one of several reached by Endo recently, will give Watson a royalty-free license on patents covering Opana ER (oxymorphone HCl) and will allow the company to launch its generic version of the drug no later than Sept. 15, 2012, Watson said this month.

Endo had originally sued Watson in March after the generic-drug maker filed an ANDA to market a generic version of Opana ER 5-, 7.5-, 10-, 15-, 20-, 30- and 40-mg tablets. The companies did not disclose financial details of the settlement.

The deal will allow Watson to bring its generic version of Opana ER to market the same day as Sandoz and Barr Laboratories, who reached settlements with Endo earlier this year (Generic Line, June 23).

Actavis, however, reached a deal with Endo last year that will allow it to bring its generic Opana ER to market more than a year earlier, in July 2011.

For Endo, the deals will allow the company to stave off immediate generic competition to the drug that, when combined with Opana, the immediate-release version of the drug, had worldwide sales of about $180 million in 2009.

Meanwhile, the company is moving to strengthen its own generics business, agreeing last month to acquire Qualitest Pharmaceuticals, the sixth-biggest generic-drug maker in the U.S., for $1.2 billion. — David Belian
IMS: Global Drug Sales to Rise In 2011 Despite Patent Losses

Although patent expirations and limits on drug spending can hamper growth of drug sales in developed countries, global pharmaceutical sales are nonetheless expected to grow 5 to 7 percent in 2011, according to an annual forecast.

The global pharmaceutical market could reach $880 billion in 2011, up from $825 billion in 2010, consulting firm IMS Health says.

That expansion is driven in part by explosive growth in China, now the world’s third largest market for pharmaceutical sales. Drug sales in that emerging market are expected to grow 25 to 27 percent next year, to more than $50 billion.

“Pharmerging” Markets

Further bolstering worldwide growth are the 17 so-called “pharmerging” countries where sales are expected to rise 15 to 17 percent in 2011. Greater access to healthcare in those markets is driving demand for medicines, which could reach $170 billion to $180 billion next year.

However, the situation in the U.S., Canada and Europe is vastly different. Substantial generic price reductions in Spain and Canada, price pressures on brands in Germany, across-the-board price cuts for brands in Turkey and Greece, and the use of pre-authorization and cost-sharing provisions in the U.S. to cut healthcare costs have served to mitigate sales growth in those markets.

That marks a change from last year, when IMS said that sales growth was boosted by a stronger-than-expected U.S. market. U.S. drugmakers’ efforts to expand access to and awareness of patient-assistance programs and their offer of copayment subsidies for needy patients also helped to limit the impact of the economic downturn, IMS said at the time.

In the coming year, though, generic competition will dampen sales for about $30 billion worth of drugs facing patent and exclusivity cliffs in the U.S. Those drugs include Pfizer’s cholesterol drug Lipitor (atorvastatin calcium), Sanofi-Aventis and Bristol-Myers Squibb’s blood thinner Plavix (clopidogrel bisulfate), Eli Lilly’s schizophrenia treatment Zyprexa (olanzapine) and Daiichi and Ortho-McNeil’s antibiotic Levaquin (levofloxacin). The last four drugs alone accounted for $17 billion in sales over the last 12 months.

However, 2011 promises a “new wave of innovation” as several specialty biopharmaceutical products, which target unmet medical need and have the possibility to significantly alter treatment paradigms, are expected to gain approval.

They include five potential blockbuster treatments for stroke prevention, melanoma, multiple sclerosis, breast cancer and hepatitis C. Those drugs are expected to expand overall drug sales, redirecting spend away from lower-cost generics.

In addition, 2011 will be a critical year to see how healthcare reform impacts pharmaceutical sales, IMS Health says. — LaCrisha Butler

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Lilly Hits Dr. Reddy’s With Suit Over ANDA for Gemzar

Eli Lilly has filed another patent-infringement lawsuit in defense of its cancer treatment Gemzar, this time against Indian drugmaker Dr. Reddy’s.

The suit, filed this month in the U.S. District Court for the Southern District of Indiana, accuses the generic-drug maker of violating Lilly’s ‘826 patent on Gemzar (gemcitabine HCl) by filing an application with the FDA to market a generic version of the drug.

Lilly is seeking a judgment declaring its patent valid and an injunction preventing Dr. Reddy’s from manufacturing or selling generic Gemzar.

The company has filed similar suits in the same court against Sicor Pharmaceuticals, now owned by Teva, and APP Pharmaceuticals for their generic Gemzar ANDAs.

The Indiana court, however, has been prevented from ruling on the validity of the ‘826 patent because of a Michigan court’s decision declaring it invalid in a case Lilly brought against Sun Pharmaceutical (Generic Line, April 14).

Earlier this year, the U.S. Court of Appeals for the Federal Circuit upheld the Michigan decision, ruling that the ‘826 patent is invalid because Lilly double-patented claims already included in its ‘614 patent on the drug (Generic Line, Aug. 4).

Lilly has asked for a rehearing of the Federal Circuit’s decision. But if the judgment stands, the company’s only remaining patent on Gemzar would be the ’614, which expires Nov. 15. The ’826 patent would expire in 2013.

If Lilly succeeds in overturning the appellate court’s decision, the Indiana court could rule on the validity of the ’826 patent, the company says.

Losing patent protection on Gemzar would be a major blow to Lilly, which loses patent protection on its best-selling drug, the schizophrenia treatment Zyprexa (olanzapine), next year.

The company also is defending its patents on the attention-deficit drug Strattera (atomoxetine HCl) (Generic Line, Sept. 15).

Gemzar had worldwide sales of about $1.4 billion in 2009, according to Lilly’s annual report. — David Belian

FDA Orders Halt to Marketing Of Unapproved Gout Drug

The FDA is giving manufacturers of unapproved generic versions of oral colchicine 45 days to stop making the gout treatments and 90 days to stop shipping them.

The move is part of an FDA initiative against marketing of unapproved drugs, announced in a June 2006 compliance policy guide, the FDA said last month.

Unapproved versions of oral colchicine — with no approved prescribing information, dosage recommendations or drug interaction warnings — have been used for many years to prevent gout, treat gout flares and treat familial Mediterranean fever.

Mutual Pharmaceutical/URL Pharma’s Colcrys is the only FDA-approved single-ingredient oral colchicine product, and the FDA has warned of potentially fatal toxicity if it is combined with drugs such as clarithromycin.

The company will continue its patient assistance and co-pay assistance programs until there is generic competition for Colcrys, the FDA says.

Since publication of the 2006 compliance policy guide, the agency has been cracking down on makers of unapproved drugs.

For example, the agency has ordered 20 companies to stop manufacturing unapproved drug products containing ergotamine tartrate and threatened enforcement action against companies marketing approximately 200 unapproved cough suppressants containing the narcotic hydrocodone, among other actions.

Two generic-drug makers also were ordered to stop making and selling unapproved nitroglycerin tablets, which are used to relieve chest pain or stop a heart attack. —April Hollis
FDA Debuts New Safety Rule For Bioequivalence Trials

To reduce the overreporting of adverse events in drug trials — including bioavailability and bioequivalence trials for generics — the FDA has issued a final rule that clarifies when and what events sponsors should report.

The overreporting of uninformative individual adverse events, often without comparative data, drains the agency’s resources and often complicates and delays its ability to detect a safety signal, the agency said in releasing the new rule and accompanying draft guidance.

The rule and guidance, published in the Federal Register last month, revise what is considered an adverse event for safety reporting to clearly distinguish when it is appropriate to submit individual or aggregated safety events.

Comments on the draft guidance should be submitted by Dec. 28. The rule becomes effective March 28.

These clarifications should increase the likelihood that submitted information will be interpretable and will meaningfully contribute to the developing safety profile of the investigational drug and improve the overall quality of safety reporting,” the FDA says in the guidance.

Under the current rule, sponsors investigating investigational new drugs are required to notify the FDA of any serious or unexpected adverse experience “associated with the use of the drug” and any finding during nonclinical studies that suggested a significant risk to humans.

As a result, sponsors frequently report, as individual cases, serious adverse events that are manifestations of the underlying disease, such as stroke or acute myocardial infarctions among an elderly study population, or serious adverse events that are study endpoints, the FDA says.

“This final rule will expedite FDA’s review of critical safety information and help the agency monitor the safety of investigational drugs and biologics,” Rachel Behrman, associate director for medical policy at CDER, says.

Under the new safety rule, events that suggest a significant risk to study participants must now be reported within 15 days of the sponsor becoming aware of an occurrence. These include serious and unexpected suspected adverse reactions.

Some events, such as angioedema, are so uncommon that they are reportable even with a single occurrence. Other events, including known consequences of an underlying disease, are reportable with one or more occurrences or in an aggregate analysis. In addition, findings from other sources — clinical, epidemiological and pooled, or meta-analysis — must be reported.

In each safety report, the sponsor must identify all safety reports previously submitted to the FDA and analyze the significance of the suspected adverse reaction.

The final rule and draft guidance are available at www.fdanews.com/ext/files/FinalRule_InvestigationalNewDrug.pdf. — LaCrisha Butler
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FDA Direct Final Rule Is Withdrawn

For Authorized Generic Drugs

The FDA withdrew its direct final rule requiring drugmakers to report information on authorized generics in NDA annual reports, delaying implementation of part of the FDA Amendments Act (FDAAA) and giving companies more time to prepare for the rule.

Under the FDAAA, the agency is required to publish a list on its website of all authorized generic drugs included in manufacturers’ annual reports. The FDA also is required to update the list quarterly and notify relevant federal agencies, including the FTC, that the list has been published. The direct final rule would have required drugmakers to list their authorized generic distributors in annual reports dating back to 1991 (Generic Line, Oct. 1, 2008).

The FDA will follow the usual rulemaking process for a companion proposed rule, which was issued in conjunction with the direct final rule last year, the agency said on its website last week.

(See Authorized, Page 2)