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Outlook

Biosimilars Policy, Patents, Antitrust, Drug Compounding Among Year's Key Topics

In 2014, the key concerns for drug and biotech companies will include biosimilars, generic drug labeling, antitrust implications of patent litigation and implementation of new authority for the Food and Drug Administration.

Bloomberg BNA contacted stakeholders and attorneys to identify the important 2014 issues for drug and biotech companies in the courts, Congress and regulatory agencies.

Among the key issues to watch will be how the FDA implements its new authorities over drug compounders and the continuing implementation of the FDA Safety and Innovation Act (FDASIA) of 2012. The 340B drug-discounts program is another area to watch as the Health Resources and Services Administration plans to issue new regulations in 2014 that address all of the major aspects of the program.

FDA Priorities. The top priorities for the FDA's Center for Drug Evaluation and Research (CDER) in 2014 include pharmacy compounding, rethinking pharmaceutical quality, improving drug labels and drug safety, Richard Moscicki, CDER's deputy director for science operations, said Dec. 11, 2013.

Moscicki, who spoke at the FDA/CMS Summit for Biopharma Executives, said other priorities include implementing FDASIA and building a modern information technology infrastructure.

For FDASIA, Moscicki said CDER is focusing on the following:

- expedited drug reviews and the breakthrough therapy designation;
- antibiotic development;
- treatments for rare diseases;
- drug shortages;
- review performance goals under the Generic Drug User Fee Amendments of 2012 (GDUFA), which was enacted as part of FDASIA; and
- electronic submissions.

''The effective implementation of review-related provisions of FDASIA remains critical,'' Daniel A. Kracov, of Arnold & Porter LLP, in Washington, said. ''Although some of the provisions are already attracting substantial interest—such as the 'breakthrough' drug provision—many of the provisions relate to optimizing the day-to-day FDA role in the 'blocking and tackling' of drug and device development and review. The agency appears to be off to a good start, but improving transparency and predictability takes time,'' he said.

With regard to the development of new antibiotics, Kracov predicted that ''we will see the enactment of provisions targeting the approval of antibiotic drugs for limited populations,'' such as is contemplated under the recently introduced Antibiotic Development to Advance Patient Treatment (ADAPT) Act of 2013, as well as other measures to support drug development in this area.

In December 2013, a bipartisan group of House members introduced the ADAPT measure (H.R. 3742) that would permit the FDA to approve antibiotics and antifungals for limited patient populations. The legislation, sponsored by Reps. Gene Green (D-Texas) and Phil Gingrey (R-Ga.) and others, would develop a pathway for antibiotics and antifungals at the FDA that permits the agency to approve drugs aimed at treating emerging threats in limited and specific populations. The legislation builds on the Generating Antibiotics Incentives Now (GAIN) Act, which was signed into law in July 2012 as part of FDASIA. The GAIN Act targets problems associated with antibiotic resistance and life-threatening pathogens.

An FDA official says new problems continue to be identified with compounding pharmacies.

''The GAIN Act may solve certain problems, but it is clearly only part of the puzzle,'' Kracov said. ''It will be interesting to see how these efforts play out. [T]hese provisions may ultimately serve as a model for incentivizing the development of innovative products addressing other serious public health concerns.''

Drug Compounding, Supply Chain. The FDA has been focusing on the drug compounding industry because of the fall 2012 outbreak of fungal meningitis caused by contaminated drugs made by the New England Compounding Center (NECC), Moscicki said. Traditionally, compounding pharmacies custom-make medications for specific patients in response to a prescription and are regulated by state boards of pharmacy. The NECC, which was based in Framingham, Mass., reportedly was producing large quantities of medications without individual prescriptions.

''New problems continue to be identified in compounding pharmacies across the country,'' Moscicki said.

Moscicki said new legislation was enacted that provides some clarity over jurisdictional issues for compounding pharmacies and adds a new category of outsourcing facilities. On Nov. 27, 2013, President Barack Obama signed into law a bill (H.R. 3204) that clarifies the FDA's authority over compounding pharmacies(11 PLIR 1438, 12/6/13). The Drug Quality and Security Act (Pub. L. No. 113-54) defines the FDA's role in the oversight of ''outsourcing'' or large-scale compounding facilities.

''FDA will be moving aggressively forward to implement this new law,'' Moscicki said. ''We will be establishing manufacturing requirements for these outsourcing facilities.''

On Dec. 2, 2013, the FDA announced steps to implement the drug compounding provisions in the Drug Quality and Security Act, including releasing two draft guidances providing information on outsourcing facilities(11 PLIR 1437, 12/6/13). Comments on the draft guidances are due by Feb. 3. The agency also asked for comments to help in the development of a list of bulk drug substances that may be used to compound drug products. Nominations for the bulk drug substances list are due by March 4.

The new law also contains track-and-trace provisions for the drug supply chain that would replace state laws with a uniform standard. The Biotechnology Industry Organization (BIO) said in a Dec. 19 statement that it ''will work with stakeholders throughout the supply chain to ensure that implementation of the new system goes smoothly.''

Cathy L. Burgess, with Alston & Bird LLP, in Washington, agreed that compounding will be a top issue, in light of the recently enacted Drug Quality and Security Act.

Although the new law exempts outsourcing facilities from certain requirements, specifically the provisions pertaining to new drug applications, track and trace, and labeling for adequate directions for use, Burgess noted that there are no exemptions from current good manufacturing practice or cGMP requirements. ''An open question is whether the agency will tailor cGMP requirements for outsourcing facilities, and how it will ensure that those requirements are equivalent in terms of ensuring drug product quality,'' Burgess said.

As to the ''track and trace'' requirements, Mary Devlin Capizzi, of Drinker Biddle & Reath LLP, in Washington, said that those requirements eventually ''will be the subject of guidance and regulations issued by the FDA.'' In addition to the U.S., many other governments have been implementing or trying to implement track and trace laws, she said. ''At the moment, global requirements are not consistent,'' Devlin Capizzi said. Accordingly, ''[a]s implementation efforts ramp up, issues of mutual compatibility and the cost of compliance will become increasingly important,'' she said.

Biosimilars. Ralph G. Neas, president and chief executive officer of the Generic Pharmaceutical Association (GPhA), said that biosimilars will continue to be a big issue in 2014 at the state, national and international levels,

They will be an issue ''in the international treaties context, in a biosimilar naming context, as well as with state biosimilar implementation,'' Neas said.

Neas said that Amgen and Genentech have pushed for biosimilar legislation in the states and GPhA and its allies have fought against it. ''Big bio and its allies'' are trying ''to use these preemptive strikes to erect barriers against future access to biosimilars in the states,'' he said.

''We're headed into 2014 in pretty good shape,'' Neas said. ''We're not going to relax. We obviously have activities ahead of us.''

''The efforts to ensure how the states are going to implement these laws are serious and that's important but so are the international treaties,'' Neas said. ''Once you have international treaties then you have harmonization of international laws so if big bio and big pharma win at the international level, then the United States has to change in some cases existing law'' and other nations could have less access to affordable medicines.

Neas said there is no indication yet of when the FDA will issue guidance on the naming of biosimilars. In September 2013, GPhA submitted a citizen petition to the FDA recommending that a biosimilar share the same name as the branded biologic (11 PLIR 1171, 9/27/13). Specifically, the petition said that all biosimilars approved by the agency should share the same international nonproprietary name (INN) as the biologic products to which they refer, because by definition they are ''highly similar'' to the reference biologics and have no clinically meaningful differences that require a unique name.

The Federal Trade Commission will hold a workshop on issues related to biosimilars, including new state rules on their use.

Unique names ''would cause much confusion and much possible chaos in terms of patient safety and access to affordable medicines,'' Neas said.

Neas said the FDA will approve a biosimilar over the next couple of years but ''we have not gotten any indication yet with respect to approval time.''

Michael Reilly, executive director of the Alliance for Safe Biologic Medicines (ASBM), said that his group also will be focusing on biosimilars at the international, state and federal levels. However, his group's stance on naming differs from GPhA's in that ASBM says biosimilars need unique names so that they can be traced back to the manufacturer if adverse events occur.

Reilly said ASBM has always felt that the FDA is leaning toward unique names. ''They're clearly ruminating on it, it's just a matter of what they're going to do,'' he said.

Reilly said the biosimilar issues in the states ''are really around the substitution issue and you're going to see a pickup from last year on the kind of inconclusive end to the biosimilar substitution discussion.'' Reilly said he doesn't expect the states to take up the naming issue.

The Federal Trade Commission ''is jumping into this discussion'' on the naming issue and state laws ''but

  PLIR ISSN 1542-9547

that is really the federal level,'' Reilly said. The FTC plans to hold a workshop Feb. 4 on biosimilars that will focus on how state regulations and naming conventions may affect the development of, and competition for, biosimilars(11 PLIR 1523, 12/20/13).

''I think at some point there has to be some action by the FDA even if it's just to clarify their position,'' Reilly said. ''I think that their silence has definitely been problematic.''

Reilly said it is important to have global standards for biosimilars ''so that we don't have a situation where, if you look at what Colombia is doing, they're considering for example, where if you're approved anywhere in the world, you're approved in Colombia. That's concerning.''

Reilly said there are a lot of competing pressures for emerging countries to relax the standards for biosimilar quality and ''I think that there will be a push to try and establish some kind of global floor, if you will, to make sure that no matter where you buy your biosimilars, they are safe.''

BIO said in its statement that it ''will work to prevent any legislative erosion of the Biosimilars Price Competition and Innovation Act (BPCIA), and continue to advocate our positions on the implementation processes at FDA and CMS [Centers for Medicare & Medicaid Services] to ensure that these agencies' regulatory and reimbursement decisions are consistent with our principles and supportive of patient safety and incentives for innovation.''

''Additionally, we will work in the states to ensure that mandatory substitution laws are adopted so that patients and physicians can be confident that the product that is provided is the one which was prescribed,'' BIO said. ''Our key principles for biosimilars include ensuring patient safety, recognizing scientific differences between drugs and biologics, maintaining the physician-patient relationship, and preserving incentives for innovation.''

''2014 should see measurable progress and clarity from FDA on the biosimilar pathway under the BPCIA,'' Terry Mahn, of Fish & Richardson's Washington office, said. ''We know that multiple biosimilar candidates are undergoing clinical testing and comparative analysis to compete with the blockbuster biologics, some of which are coming off patent protection,'' he said, adding that the FDA is behind in getting information and guidance out to industry because it is learning on the job just like the biosimilar applicants themselves.

Sandoz's Case. In November 2013, the U.S. District Court for the Northern District of California dismissed Sandoz Inc.'s declaratory judgment action for noninfringement and invalidity on patents covering Amgen's rheumatoid arthritis treatment Enbrel (etanercept), finding that the BPCIA's requirements governing biosimilar approvals at the FDA precluded the court from hearing the patent dispute until after the parties had engaged in the statutorily mandated exchanges of information required by the 2010 law.

In December, Sandoz appealed the district court's dismissal to the U.S. Court of Appeals for the Federal Circuit (11 PLIR 1509, 12/20/13).

''The *Sandoz* decision and the approval of biosimilar monoclonal antibodies in Europe suggest that the first application under the BPCIA will be coming in the not too distant future,'' George Yu, at Schiff Hardin, in San Francisco, said.

And Jay R. Deshmukh, of Knobbe Martens Olson & Bear LLP, in Washington, predicted that ''issues surrounding the biologics portion'' of the Affordable Care Act, which contains BPCIA, ''will be the biggest [issues], with both short and long term impact. Like the recent *Sandoz* case from California, these issues/decisions could involve intellectual property matters or other regulatory issues such as substitutability.''

Generic Drug Labeling. GPhA's Neas also said that generic drug labeling will be a big issue in 2014 because of the FDA's proposed rule that would allow generic drug manufacturers to use the same process as brand drug manufacturers to update safety information in product labeling.

A notice announcing the proposed rule was published in the Nov. 13, 2013, Federal Register (78 Fed. Reg. 67,985)(11 PLIR 1369, 11/15/13). The FDA subsequently extended the comment period on the proposed rule until March 13.

According to the FDA, the proposed rule would speed the dissemination of new safety information about generic drugs to health professionals and patients.

''This will go to the top of the priority list with respect to GPhA's agenda in 2014,'' Neas said.

''GPhA is very concerned that multiple versions of critical safety information would lead to unnecessary confusion and uncertainty for prescribers and other healthcare professionals, with harmful consequences for patients,'' Neas said in a statement when the rule was published.

An FDA proposed rule allowing generic companies to change safety-related labels on drugs is seen as having potential to cause confusion about drug safety.

Neas said that in the proposed rule the FDA acknowledges that there could be temporary differences in labeling for drugs that the agency has determined to be therapeutically equivalent, especially if multiple abbreviated new drug application (i.e., generic) holders submit labeling changes that differ from each other and the branded drug.

''We are working with the FDA and other stakeholders to make sure patient safety is prioritized and that any changes to generic labeling rules would not undermine public confidence in the safety and efficacy of generic medicines or undo 30 years of growth in generic drug use,'' Neas told said . ''We're very concerned that multiple versions of safety information would lead to confusions and uncertainty for prescribers and other health-care professionals with harmful consequences for patients.''

''We are doing everything possible to make sure that uniform information continues,'' Neas said.

Neas said GPhA will be putting together ''extensive'' comments on the proposed rule.

Alston & Bird's Burgess said the FDA's proposed rule on generic drug safety-related product labeling will be an important issue in 2014. ''The proposed rule has the potential to create confusion regarding the safety of prescription drug products—generic and branded—and possibly result in constant revision of product labeling,'' she said.

Drug Shortages. ''There has been a lot of progress on drug shortages over the last year,'' Neas said. The generic drug industry group is committed ''to a multi-stakeholder operation'' to combat drug shortages, he said.

''According to the FDA, progress is being made with respect to drug shortages,'' Neas said. In October 2013, the FDA put out a strategic plan to help prevent drug shortages, and also proposed a rule that would require drug manufacturers to report any supply chain disruptions, with comments due in January (11 PLIR 1339, 11/8/13).

''More can and will be done to ensure timely patient access to medications,'' Neas said. ''The original causes of drug shortages are multifaceted and involve manufacturers, regulators and distributors but we're convinced that the solution is attainable provided that all members of the drug supply chain continue to work together. That has been the case, increasingly so, over the last two years.''

Neas said GPhA's other priorities in 2014 include:

- risk evaluation and mitigation strategies (REMS);
- generic and biosimilar utilization at the national and state levels for programs such as Medicare and Medicaid and the Department of Veterans Affairs;
- any efforts at the state level to weaken existing law and carve out exceptions for various products; and
- continuing to meet with top FDA officials to address biosimilar issues, generic drug user fees implementation, quality and compliance issues.

340B Program. Maureen Testoni, general counsel of the Safety Net Hospitals for Pharmaceutical Access (SNHPA), said that the Health Resources and Services Administration (HRSA) ''has published a notice that they intend to come out with a comprehensive 340B regulation in June of 2014.''

Created in 1992, the 340B program requires pharmaceutical manufacturers participating in the Medicaid program to have an agreement with the Department of Health and Human Services under which the manufacturer provides discounts on covered outpatient drugs purchased by safety-net providers such as disproportionate share hospitals and federally qualified health centers.

''Our understanding of that regulation is that it will address all of the major aspects of the 340B program and that the intent of it is to put into regulation a lot of the guidance that has been released over the years in an informal manner,'' Testoni said. ''Right now there are virtually no regulations for 340B. There is just one regulation that pertains to orphan drugs that was just finalized in October.''

''There have been a number of informal guidances addressing issues such as ''the patent definition or contract pharmacy,'' Testoni said. ''We understand that this comprehensive regulation is seeking to put a lot of that guidance into regulation.''

''We also expect that part of putting that into regulation will be to address some of the issues that have come up over the years related to 340B. Like, for example, with patient definition, there have been concerns that some of the language has been gray,'' Testoni said. ''It hasn't always been clear what HRSA's intent was and so we're expecting that when they put forward this regulation and they propose it that they will also address some of those aspects of where the guidance has been unclear in the past.''

Orphan Drugs and 340B. In July 2013, HHS issued a final rule clarifying the types of discounts available on rare disease, or ''orphan,'' drugs when purchased by safety net providers under the 340B drug program(11 PLIR 916, 7/26/13). The rule became effective Oct. 1, 2013.

In the final regulation on orphan drugs, ''they are interpreting the provision to allow the use of 340B pricing when a drug is used for a purpose other than its orphan indication,'' Testoni said. ''So, for example, you might have a drug like Remicade that has an orphan designation for Crohn's disease but it is used primarily to treat rheumatoid arthritis. So under the regulation, you will be able to use 340B pricing when you're buying that drug to treat rheumatoid arthritis but you would not be able to use 340B pricing when you are buying that drug to treat Crohn's disease.''

''And the reason behind that is that when you look at the statute it really focuses on the fact that a drug was designated an orphan drug and you're only designated orphan for a particular disease. HRSA was making it clear that the 340B restriction only applies to the orphan disease,'' Testoni said. ''We support that. We think that is an appropriate way to interpret the statute.''

Ted Slafsky, president and chief executive officer of the SNHPA, also said that another issue for the 340B program is that the Pharmaceutical Research and Manufacturers of America (PhRMA) sued HRSA after they released their regulation on the orphan drug exemption.

On the PhRMA lawsuit, Testoni said, ''The briefing on that is going on right now and the court has set a deadline for the middle of January by which everybody has to have all of their briefs submitted. Then the court will come out with a decision. I expect the decision to come relatively quickly after that. I think that by March we'll have a final ruling on that. If the court does not side with PhRMA, it is possible that PhRMA will then appeal and it could go on longer.''

When asked whether he thinks there will be legislation on 340B in 2014, Slafsky said ''there was some talk about'' it at the beginning of 2013, but there wasn't any legislation introduced.

''While the drug industry had some momentum at the beginning of this year, pushing for restrictions on the program, we believe that the 340B champions have successfully fought back,'' Slafsky said.

Testoni said she expects that there will be more auditing in the 340B program. ''There will be more auditing by HRSA for the providers,'' she said. ''I think that there will be more auditing by drug manufacturers of providers but I'm not 100 percent sure of that yet because the drug manufacturer audits that have occurred, they haven't been released so we don't know if they're really finding issues and reaping any benefit. I would

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expect that they would need to see some benefit in order for them to continue doing the audits.''

''We're hopeful that, and we're certainly advocating that, HRSA will audit manufacturers but there has not been any audit of a manufacturer so far even though there have been well over 100 audits of covered entities,'' Testoni said. ''HRSA is required under the law, as part of health care reform, to do periodic audits of manufacturers so we're expecting them to do that.''

BIO said in its statement that ''growing evidence suggests the expanded 340B program has departed significantly from its original intent, leading to evidence of abuse of the program and unintended and potentially harmful consequences for patients.''

''We will work with the Health Resources and Services Administration (HRSA) to improve oversight, and help ensure program integrity,'' BIO said.

Sunshine Act, Drug Marketing. John Kamp, executive director of the Coalition for Healthcare Communication, said that the implementation of the Physician Payments Sunshine Act will keep him busy in 2014.

Under the sunshine law—which is part of the Affordable Care Act—applicable manufacturers are required to report payments or other transfers of value they make to physicians and teaching hospitals to the CMS. Data are due to be reported to the CMS by March 31 and the CMS said it will release the first year's data on a public website by Sept. 30.

''I'm particularly concerned about the treatment of textbooks and reprints as reportable items,'' Kamp said.

Kamp also said he expects the FDA to issue some guidance on social media. The agency has a July deadline to issue guidances, he said. The FDA is required by FDASIA to issue specific guidance on social media by July 9, 2014.

''The FDA issue that I think is very interesting, we'll see if it plays out in 2014 or not, has to do with the impact of the *IMS* and *Caronia* court cases,'' Kamp said. These cases ''bring the First Amendment to play in drug marketing regulation.''

Recent cases in the courts have brought the First Amendment into play in the regulation of pharmaceutical marketing.

''If that plays out the way I suspect it might, FDA's going to have to change its rules on off-label marketing,'' Kamp said. ''But FDA has been incredibly good over the last 15 years at avoiding dealing with it head on.''

On Dec. 3, 2012, the U.S. Court of Appeals for the Second Circuit found that the criminalization of truthful, nonmisleading promotion of FDA-approved pharmaceuticals violates the First Amendment (*United States v. Caronia,* 2d Cir., No. 09-5006-cr, 12/3/12) (10 PLIR 1525, 12/7/12). ''We conclude simply that the government cannot prosecute pharmaceutical manufacturers and their representatives under the [Federal Food, Drug, and Cosmetic Act] for speech promoting the lawful, off-label use of an FDA-approved drug,'' the majority opinion said. The appeals court also reversed the conviction of pharmaceutical company sales representative Alfred Caronia for promotion of an unapproved use of a drug.

In *Sorrell v. IMS Health Inc.*, 131 S. Ct. 2653, 2672 (2011), the Supreme Court declared unconstitutional a Vermont statute that prohibits pharmacies from selling or disclosing prescriber-identifying information for marketing purposes and that precludes pharmaceutical manufacturers from using such information to market their products (9 PLIR 771, 6/24/11). The high court found the ban an impermissible restriction on free speech.

According to Arnold & Porter's Kracov, the interplay between ongoing Department of Justice and FDA off-label enforcement ''and the First Amendment will continue to be important'' in 2014.

The government, Kracov said, ''is attempting to avoid another negative ruling on pharmaceutical company speech First Amendment protections, particularly a negative Supreme Court decision that could undermine fundamental assumptions about FDA regulatory authority over industry communications.''

He said that while the government has attempted to minimize the importance of the *Caronia* decision, ''it has to be top of mind when formulating the agency's regulatory activities in this area, such as the development of guidance on topics such as industry scientific exchange and social media.''

''Another result of the developing First Amendment case law has been an emphasis on other bases for enforcement and False Claims Act claims, including kickback, pricing and cGMP violation-based actions,'' he said. ''These developments—combined with the rapid evolution of heightening standards for pharmaceutical compliance in various jurisdictions around the world—will only make having an effective global compliance program even more important than it is today.''

Linda D. Bentley, of Mintz, Levin, Cohn, Ferris, Glovsky & Popeo PC, in Boston, agreed that the pharmaceutical industry must focus on compliance programs as the FDA and state attorneys general will continue to focus on enforcement actions for a variety of alleged illegal activities, including cGMP problems (in the U.S. and elsewhere), off-label promotions and false claims. ''From the perspective of the states, these actions are attractive because they often result in multimillion-dollar settlements,'' she said. ''The FDA does not see the same direct financial benefits, but enforcement is part of its mission and it has to be active in this area to avoid or at least minimize the types of beatings that it got as a result of the compounding pharmacy debacle.''

Kathleen McDermott, of Morgan, Lewis & Bockius LLP, in Washington, similarly predicted 2014 would bring ''[i]ncreased litigation of whether regulatory violations may comprise a false claim and, if so, what is the parameter of such a theory.''

Moreover, she said, ''The conventional approach of express and implied certification related to conditions of payment or participation is wearing thin as a predictable judicial benchmark under False Claims Act jurisprudence. Generally, the judicial decisions appear to be concerned whether the alleged violation is material to payment.''

She also said the *United States ex rel. Nathan v. Takeda Pharm. N. Am.* case, which is awaiting a decision on certiorari from the Supreme Court (11 PLIR

1222, 10/11/13), involves a federal circuit court split concerning the level of specificity about false claims that must be alleged in an FCA complaint. Not only is the case of interest for its articulation of the Federal Rule of Civil Procedure 9(b) standard, she said, but also challenges to what extent a regulatory violation may be pled as a false claim and, if so, what must constitute sufficiency for pleading.

McDermott also predicted that other False Claims Act litigation will focus on interpreting amendments related to the scope and definition of claims. And, she said, ''relator litigation will explode, providing opportunities to litigate the duration of seals, public disclosure and other important process issues.''

Jacqueline C. Wolff, of Manatt Phelps & Phillips LLP, in New York, predicted continued growth in whistleblower actions brought under the FCA. ''As the government enforcement budget shrinks, the government needs to rely more and more on other avenues for developing cases,'' she said. ''Also, the pharma industry is shrinking somewhat in terms of employees due to big pharma mergers, more layoffs, more qui tams.''

While Wolff observed that most large pharmaceutical companies already have fairly robust promotion compliance mechanisms in place, ''as drugs come off-patent, the need to market versus the competition becomes more fierce. That may result in more of a violation warranting an FDA letter violating comparison rules rather than off-label promotion laws.''

In addition, she said, regarding enforcement of the Foreign Corrupt Practices Act, having already investigated many of the large pharmaceutical companies over FCPA issues, the Justice Department may start to investigate ''middle market pharma or the biotech companies conducting clinical trials overseas.'' While many such companies have paid heed to the statute, some have not, figuring that they are low-risk because they are not engaging in marketing and promotion, she said.

An attorney says the expanded scope of manufacturing standard liability puts drug companies at greater risk of being targeted in an enforcement action.

Burgess predicted that in 2014, ''we will see more enforcement actions related to supply chain management.'' FDASIA significantly expanded the FDA's regulatory reach by incorporating quality risk management oversight and controls into the agency's cGMP authority, she said. ''Under the new provisions in the law, if a finished-product manufacturer fails to establish oversight and controls related to raw materials, components and contract manufactured finished products, its distributed products are deemed to be adulterated and the introduction of those products in interstate commerce is a prohibited act. By expanding the scope of potential cGMP liability, FDASIA places finished-product manufacturers at a greater risk of being a target of investigation or enforcement action carried out by the FDA or DOJ,'' she said.

McDermott similarly predicted an increase in investigations related to quality issues, including manufacturing, clinical compliance and other FDA regulatory compliance issues.

Burgess said it is likely that the FDA will use its expanded authority under FDASIA to be more aggressive in enforcement of manufacturing quality issues.

''Because an inspection refusal now causes a drug to be adulterated, an inspection refusal could serve as the basis for an *in rem* seizure proceeding, import alert or other enforcement action based on the introduction of adulterated product into interstate commerce, which is also prohibited under'' the Federal Food, Drug, and Cosmetic Act, Burgess said, noting that the agency has already started to embrace its new authority. ''During the summer of 2013, the FDA imposed import alerts and issued two warning letters citing violations for delaying, denying, limiting or refusing to permit an inspection,'' she said. ''We can expect the FDA to continue exercising this new authority in 2014.''

Bentley, of Mintz Levin, noted the increasing activity of nongovernment lawyers in bringing class actions based on alleged violations of FDA requirements. These actions often are filed under consumer protection laws, particularly in states such as California, she said.

In May 2013, generic drug manufacturer Ranbaxy USA Inc. paid $505 million to settle allegations of false claims to federal and state health-care programs for substandard drugs distributed from its facilities in India (11 PLIR 626, 5/17/13). Burgess said that settlement, which was $237 million in federal civil claims, $118 million in state civil claims and $150 million in criminal fines and forfeitures, likely signals a new trend in FCA and criminal enforcement.

''The government's aggressive efforts with respect to off-label promotion of drugs and medical devices have had a significant impact on medical product promotional activities,'' she said.

Antitrust, Pay-for-Delay. The Federal Trade Commission is expected to continue to challenge pay-for-delay agreements in drug patent litigation.

During a Dec. 3, 2013, hearing of the House Energy and Commerce Committee's Commerce, Manufacturing and Trade Subcommittee(11 PLIR 1444, 12/6/13), Rep. Jan Schakowsky (D-Ill.) applauded the FTC's ''frontline'' approach in ''protecting both consumers and businesses from unfair, deceptive, fraudulent or anticompetitive practices.'' Schakowsky is the ranking minority member of the subcommittee.

Schakowsky said she was ''particularly pleased'' that the agency has focused on access to lifesaving drugs. She noted that the FTC fought against pay-for-delay agreements in drug patent litigation and expressed gratitude for the outcome and the agency's efforts in the Supreme Court's *Actavis* case—calling the decision that ''reverse payment agreements can violate antitrust laws'' a ''big win for consumers.''

In June 2013, in the *FTC v. Actavis* decision, the Supreme Court said the legality of drug patent settlements should be evaluated under the ''rule of reason'' approach, but didn't hold such agreements to be presumptively illegal(11 PLIR 771, 6/21/13).

Scott Burwell, with Finnegan, Henderson, Farabow, Garrett & Dunner LLP, in Reston, Va., said that it will be interesting in 2014 to see whether Congress will pass legislation addressing settlement of drug patent cases,

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and how courts will apply the rule of reason in such cases post-*Actavis*.

James M. Burns, with Dickinson Wright, in Washington, agreed. The lower courts' implementation of the Supreme Court's *Actavis* decision ''is an extremely significant issue for 2014,'' he said, noting that the high court's decision left ''ample room for interpretation by the lower courts.''

''I think the *Actavis* decision will ultimately lead to a big reduction in the number of reverse payment settlements,'' Yu, of Schiff Hardin, said.

Meanwhile, Burns said, recent signals from the FTC indicate that ''the FTC is serious about continuing to be quite active in the 'pay for delay' area going forward.''

''The FTC (both Chairwoman Edith Ramirez and Bureau of Competition chief Deborah Feinstein) have publicly declared that pay for delay cases will continue to be a 'top priority' for the FTC,'' he said. ''Accordingly, we can expect continued activity from the FTC on this issue—bringing cases, writing amicus briefs, and supporting legislation aimed at combating 'pay for delay' settlements,'' Burns added.

Burns said he wouldn't be surprised to see legislative action on ''pay for delay'' settlements in 2014. Such legislation could well be advanced in 2014, particularly depending on the way in which the lower courts begin to interpret *Actavis*, he said.

On Dec. 11, 2013, Rep. Bobby L. Rush (D-Ill.) introduced a bill (H.R. 3709) that would prohibit branded drug companies from compensating generic drug companies to delay the entry of a generic drug into the market. The Protecting Consumer Access to Generic Drugs Act of 2013 was referred to the House Energy and Commerce and Judiciary Committees for consideration.

Other Antitrust Issues. Burns said that ''pay for delay'' likely will be the most significant type of pharmaceutical antitrust litigation in 2014. Other alleged methods of stifling generic drug competition will continue to be ''hot topics,'' including product-hopping, deals in which a branded company agrees not to sell an authorized generic, as well as denial of access to branded samples.

Indeed, the FTC has filed an amicus brief in opposition to using risk evaluation and mitigation strategies (REMS) to delay the creation of generics by refusing to provide branded samples. The FTC filed the brief in the U.S. District Court for the District of New Jersey in March 2013, in the *Actelion Pharmaceuticals v. Apotex* case (11 PLIR 323, 3/15/13).

All of these issues will continue to work their way through the lower courts in 2014, Burns said.

In addition, Burns said, new rules requiring pharmaceutical companies to obtain the approval of the FTC before transferring ''all commercially significant rights'' to a drug in a licensing agreement will have a major impact in 2014. These changes, which took effect Dec. 16, 2013, ''will slow the pace of such transactions and ensure that greater scrutiny of the competitive implications of all such transactions will occur,'' he said.

Patents. Patent reform continues to be an issue for the pharmaceutical/biotechnology industries. BIO said ''patents are often the main assets of small biotech companies, and they rely on this intellectual property to attract investors to fund the lengthy and expensive R&D process necessary to bring new therapies to market.''

''We will work to ensure that patent reform improves the efficiency, objectivity, predictability, and transparency of the patent system,'' BIO said in a statement.

In the area of patent law, Finnegan's Burwell said that in 2014, the Supreme Court could take up the issue of indirect infringement. ''The law of indirect infringement has received considerable attention from the Federal Circuit recently, and certiorari petitions involving this issue are currently pending before the Supreme Court,'' he said. ''Should the Supreme Court grant certiorari in one or more of these cases, its resolution of this area of the law may have significant ramifications for Hatch-Waxman litigation involving method patents.''

In addition, Burwell said, as a result of the America Invents Act signed into law in 2012, generic drug manufacturers may wind up increasingly using inter partes review proceedings as an adjunct to traditional Hatch-Waxman litigation.

Yu agreed. ''The availability of meaningful post-grant challenges to patents, as well as the implementation of the first-inventor-to-file provisions of the AIA could lead to new strategies of challenging patents that are important in the pharmaceutical industry,'' he said.

Mahn, of Fish & Richardson, said recent decisions in cases like *Mayo Collaborative Services v. Prometheus Laboratories, Inc.* and *Association for Molecular Pathology v. Myriad Genetics, Inc.*, which found certain types of screening methods and genomic screening to be nonpatentable subject matter, ''have set back developments'' in the diagnostic screening and assay business.

The Supreme Court's Actavis decision is seen as leading to a potential reduction in the number of reverse-payment patent lawsuit settlements.

In *Prometheus*, decided in March 2012 by the Supreme Court, the high court, in a unanimous decision, held that certain medical diagnostic claims aren't patentable. In the *Association for Molecular Pathology v. Myriad Genetics, Inc.*, decided in June 2013, the Supreme Court ruled that isolated DNA isn't eligible for patenting but that genetic materials created ''synthetically'' are patent-eligible.

''If the pharma industry is expected to invest in technologies that will lead to more personalized medicine, they will need to protect those investments. Without patent protection, it will be very difficult to attract the capital investment that will be needed,'' Mahn said.

Hatch-Waxman Safe Harbor. Also on the patent front, in 2013, the Supreme Court declined to review two cases questioning the extent of the Hatch-Waxman Act's safe harbor provision on infringement: *Momenta Pharmaceuticals, Inc. v. Amphastar Pharmaceuticals, Inc.* (11 PLIR 830, 7/5/13), and *GlaxoSmithKline v. Classen Immunotherapies, Inc.* (11 PLIR 69, 1/18/13).

The safe harbor applies to nonsales activities of a generic drugmaker. *Classen* holds that the ''safe harbor'' provision from patent infringement applies only to research a company undertakes before FDA approval of a

drug, while *Momenta* holds that post-approval studies that are reasonably related to the development and submission of information to the FDA also would fall under the safe harbor provision.

Momenta was ''a terrible decision for biologic drug manufacturers as it effectively nullifies process patents,'' Mahn said.

''While the safe harbor should be applicable for certain post-approval activities, it should never apply to a commercialized drug product,'' he said.

Because the decisions by the Federal Circuit in *Momenta* and *Classen* arguably were in conflict about extending safe harbor protection to other activities, particularly to those that might occur after FDA approval, Yu predicted that the high court may yet take up the issue.

''Given the differences in the *Momenta* and *Classen* decisions from the Federal Circuit, I expect that the Supreme Court will review the scope and extent of the safe harbor.''

'Skinny' Labeling. Mahn predicted that in 2014, brands will start to fight back against so-called ''skinny-labeled'' generics by bringing infringement suits against generics.

''As compound patents expire, more and more drug development is being protected by method of use patents,'' he said. ''Under Hatch-Waxman, generics are allowed to carve use patents out of their labels—i.e. 'skinny' their labels—and still receive an AB rating from the FDA, provided they do not market their drugs for the patent-protected use.''

Because an AB-rated generic is fully substitutable for the brand for all approved uses, such skinny labeling effectively nullifies the brand's method of use patent, he said. This practice costs brand manufacturers billions in lost profits on new drug discoveries every year, he said.

PhRMA's Goals. In 2014, PhRMA ''will remain committed to efforts to improve the quality of patients' lives, increase the availability of new medical treatments and support the discovery of medicines and cures by biopharmaceutical research companies,'' Matthew Bennett, senior vice president of PhRMA, said in a Dec. 19, 2013, statement.

''Innovative medicines play a vital role in delivering better health outcomes and savings to the U.S. health care system,'' Bennett said. ''As we approach 2014, the promise of these medicines and ongoing scientific progress has never been greater for patients in need. Critical to turning this hope into action is ensuring patients have access to life-saving and life-enhancing medicines.''

According to its website, PhRMA is committed to preventing drug shortages.

''Pharmaceutical manufacturers have stepped up the voluntary reporting of anticipated events that could lead to drug shortages,'' the website said. ''The biopharmaceutical industry will continue to work with FDA and other stakeholders to improve upon existing reporting requirements.''

The group also is committed to combating counterfeit drugs, the website said.

''PhRMA members remain committed to rooting out criminal networks and putting a stop to the global counterfeit medicine trade,'' the website said. ''PhRMA and America's pharmaceutical industry will continue to work with public and private partners in the fight against this growing epidemic to help protect the safety and integrity of our closed drug supply system.''

PhRMA also said on its website that when it comes to funding for the FDA, it will ''continue working to help advocate for robust congressional appropriations to assist the agency in strengthening its scientific base.''

BIO said that ''increased funding for the FDA will help bring novel, safe and effective treatments to patients and promote U.S. economic competitiveness.''

''Furthermore, we will work to ensure that user fees are exempt from sequestration and instead dedicated to the review of new drugs, biologics, and medical devices in an efficient and timely manner as negotiated under FDASIA,'' BIO said.

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