Exhibit 1
Identifying 11 Leading Food and Drug Lawyers

They’re the cure for what ails the drug manufacturers, the food producers, their trade associations, and their public interest watchdogs. In the D.C. metropolitan area, no one else in private practice knows the law on food and drugs better than these 11 attorneys.

Feeling queasy over some new regulation out of the Food and Drug Administration? They know the agency (at least seven of them did time inside). Getting heartburn from the esteemed senator’s latest proposal? They know the Hill. Temperature spiking due to a competitor’s newest foray into the market? They know the case law.

How did Legal Times pick them? We solicited suggestions from our readers and our reporters. Then, freelance journalist Jenna Greene (formerly an editor at Legal Times) called experts in practice and in business to ask for further suggestions, to learn more about who does what for whom in corporate America, and to narrow down the list to Washington’s top attorneys.

To learn more about the Leading Lawyers series, including how to nominate attorneys for next year’s reports, visit www.legaltimes.com.
Food & Drug 2005: The Best Medicine

09-19-2005

Robert Brady
Robert Brady of Hogan & Hartson.

Nancy Buc
Nancy Buc of Buc & Beardsley.

Richard Cooper
Richard Cooper of Williams & Connolly.

Richard Frank
Richard Frank of Olsson, Frank and Weeda.

Mark Heller
Mark Heller of Wilmer Cutler Pickering Hale and Dorr.

Peter Barton Hutt
Peter Barton Hutt of Covington & Burling.

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Daniel Kracov
Daniel Kracov of Patton Boggs.

Bert Rein
Bert Rein of Wiley Rein & Fielding.

Peter Safir
Peter Safir of Covington & Burling.

William Schultz
William Schultz of Zuckerman Spaeder.

William Vodra
William Vodra of Arnold & Porter.
Robert Brady

Jenna Greene

09-19-2005

New drugs don't win approval simply because the company hires a clever lawyer, says Robert Brady. The Food and Drug Administration focuses on the scientific data — and the agency "gets it right the vast majority of the time."

What a smart attorney can do, says the Hogan & Hartson partner, is help companies "shape their data and approval strategy" for a smooth review by the FDA.

With eight years of experience inside the agency, Brady, 58, is well equipped to offer such advice, on everything from biologic medicines to orphan drugs. He also counsels on advertising and promotional practices.

"He is extremely knowledgeable about FDA regulations and laws, but more importantly, he understands how the agency actually works," says Dr. Steven Gould, CEO of Northfield Laboratories Inc.

For the past three years, Brady has been advising the company on its development of an oxygen-carrying blood substitute. It's uncharted territory — the FDA has never approved such a product. "Many companies have tried and failed, but we've gotten further than anyone," Gould says. Northfield is now in a Phase III trial of its product, PolyHeme.

"To get to this point we really needed Bob's input," Gould says.

Last month, Brady helped win FDA approval for another biologic product — a category that includes blood products, vaccines, and products derived from human cells and tissues. Made by Tercura Inc., the drug, Inrelex, was approved Aug. 30 after a priority review. It is a variation of human growth hormone and is used to treat children with extremely short stature.

Tercura board member Michael Astrue describes Brady as "terrific, a first-class lawyer and person."

As the former general counsel of Biogen Inc., Astrue has worked with Brady for more than 10 years. Biogen tapped Brady as lead regulatory counsel in a 1995-96 battle with the German company Schering AG over the drug Avonex, used to treat multiple sclerosis. "We won everything," says Astrue, who praises Brady for his mastery of the law and expertise on biologics.

Both Avonex (at the time of approval) and Inrelex are considered "orphan drugs" — generally that means fewer than 200,000 people in the United States suffer from the disease that the drugs target. Under the Orphan Drug Act, the FDA grants seven years of market exclusivity as an incentive for pharmaceutical companies to develop such drugs.

Brady estimates that about half of his practice involves "counseling companies on various approval pathways."

He also advises companies on advertising and promotional matters as well as crisis management issues. For about seven years the Genzyme Corp. has turned to Brady for such assistance, says chief compliance officer Roger Louis. According to Louis, Brady excels at "taking complex rules and making them simple and actionable for clients."

But Brady is more than a good lawyer. "He's a really good nonlawyer as well," Louis says. That is, he's approachable, he speaks the language of businesspeople, and he "takes the time to listen and make sure he knows what the problem or issue is before he starts dispensing advice."

the Maryland Court of Special Appeals and then for Judge James Wray of the Maryland Circuit Court for Ann Arundel County.

Brady joined the FDA chief counsel’s office in 1975. Over the next several years he served as associate chief counsel for biologics, foods, and enforcement.

From 1981 to 1983, Brady was executive assistant to acting FDA Commissioner Mark Novitch and then to FDA Commissioner Arthur Hull Hayes. The biggest issue at the time, he recalls, was the poisoning of Tylenol capsules with cyanide. “It was a real crisis. People were afraid to use their medicines,” he says.

Brady signed on as general counsel of the Cosmetic, Toiletry and Fragrance Association in 1984. Later, he became the association's executive vice president, and he continues to advise companies in the cosmetics field today.

In 1988, Brady joined then-Patton, Boggs & Blow as a partner; he moved to Hogan & Hartson in 1995. He now heads Hogan's 15-lawyer pharmaceutical/biotechnology practice. Notable colleagues include David Fox, Jonathan Kahan, Edward Korwek, and Richard Silverman.
Nancy Buc

Jenna Greene

09-19-2005

"Everything one could ask for in a lawyer" — that's how one of Nancy Buc's clients sums up the 61-year-old founding partner of Buc & Beardsley and former chief counsel of the Food and Drug Administration.

"She's extremely smart and incisive, and capable of thinking through what can and cannot be done — and what should and should not be done," continues Sandra Arnold, vice president of corporate affairs for the Population Council.

Buc worked with the international nonprofit organization in winning FDA approval in 2000 of mifepristone (known in Europe as RU-486), which induces abortion early in pregnancy. More recently, Buc helped the Population Council intervene in a Judicial Watch lawsuit filed under the Freedom of Information Act seeking certain FDA records pertaining to mifepristone. The FDA successfully argued that it has released all responsive records. The case is now before the U.S. Court of Appeals for the D.C. Circuit.

Much of her practice, Buc says, entails "working with clients to try to help them get their products approved and negotiate terms." She describes the work as "very client-specific and fact-specific."

Clive Meanwell, chairman and CEO of the Medicines Co., says he first turned to Buc when his company was having a difficult time getting the FDA green light for Angiomax, a blood thinner used in patients undergoing coronary angioplasty procedures. Buc played a "huge role" in securing FDA approval in December 2000, says Meanwell.

"But the real trick," he adds, "is to get Nancy involved in planning, not just salvaging." Buc now regularly advises the company on strategy and compliance issues. "She's sharp as a tack," Meanwell says. "She has a profound understanding of the law — not only the content, but the principles."

Buc also helps brand-name drug makers fight off generic challenges. In 1997, she represented Wyeth-Ayerst Laboratories, the maker of Premarin, a hormone replacement product and, at the time, one of the most-prescribed drugs in the United States.

Barr Laboratories Inc. and Duramed Pharmaceuticals Inc. (the companies have since merged) both sought FDA approval to market a generic version of Premarin, which Buc describes as "a very complex little drug." The question was whether the would-be generics were truly equivalent, since they did not contain all the estrogens found in the brand-name version. Ultimately, the FDA refused to approve the generic versions.

Buc earned her law degree from the University of Virginia in 1969, one of just seven women in a class of 250. Her first job as a lawyer was with the Federal Trade Commission, mainly, she says, because it was one of the few places interested in hiring women in 1969. She quickly rose to become assistant director of the Bureau of Consumer Protection — the first woman and, at the time, the youngest person ever to serve as assistant director of an FTC bureau.

In 1972, Buc joined Well, Gotshall & Manges in New York. She made partner in 1977 — the first woman partner at the firm — and then returned to Washington to open Well, Gotshall's D.C. office in 1978.

She was lured back into government in 1980 by an old friend from the FTC, Jodie Bernstein, who had become general counsel of the Department of Health and Human Services. Bernstein recruited Buc for the post of FDA chief counsel, a job Buc held from February 1980 until January 1981.

One of the biggest issues on her watch was the outbreak of toxic shock syndrome. Buc negotiated the consent

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decree with the Procter & Gamble Co. to remove a brand of tampons associated with the illness from the market. She also set the stage for the approval of alpha fetoprotein diagnostic kits, used to assess the likelihood of birth defects in fetuses. And she finalized the rule requiring drug companies to provide information directly to patients about prescription drugs.

Buc returned to Well, Gotshal in 1981. But as she neared her 50th birthday, she says, "I was getting restless," so she and colleague Kate Beardsley decided to strike out on their own in 1994.

Their D.C. firm has grown to eight lawyers. "Kate and I have built a great practice giving personal attention and practical advice to clients who need assertive advocacy at FDA and in the courts," says Buc. "We've had fun doing it, and we're still having fun."
Richard Cooper
Jenna Greene
09-19-2005

"The Easter Bunny chief counsel sent by Idi Amin" — that’s what staff at the Food and Drug Administration affectionately dubbed Williams & Connolly partner Richard Cooper during his stint in the late 1970s as the agency’s top legal officer.

"Easter Bunny" was a reference to Cooper’s only prior food-and-drug case, in which he represented a company that made holiday-themed chocolates. As for the infamous Idi Amin, Cooper spent a year with the International Legal Center in Uganda in the early 1970s.

These days, Cooper, 62, is known as a top-notch food-and-drug litigator, the man who persuaded the U.S. Supreme Court that the FDA had no authority to regulate tobacco.

"He’s such a strong litigator," says Tom Haughey, general counsel of the Par Pharmaceutical Cos. Cooper is representing the generic-drug maker in massive litigation pending in Boston federal court over the average wholesale price of prescription drugs. In a series of cases, dozens of pharmaceutical companies are alleged to have illegally manipulated prices for medicines.

Haughey praises Cooper for his intelligence, responsiveness, and efficiency. "He doesn’t make a mountain out of a molehill," says Haughey. "He’s particularly good at bringing a reasonable amount of assets to any litigation. He makes sure costs and benefits have a good relation."

Another current client is Barr Laboratories Inc. Among other issues, Cooper is advising the company on the controversial emergency contraceptive Plan B. In 2004, the FDA rejected Barr’s application to make the pills available without a prescription. An amended application is pending.

Fred Killion, Barr’s general counsel, calls Cooper "a brilliant lawyer. He brings great judgment and intellect to problem solving." Killion also highlights Cooper’s integrity and credibility: "When Richard Cooper is speaking on your behalf, people know he’s making a fair and honest presentation. He’s a very aggressive advocate, but he plays by the book."

Steve Gersten, the head of Abbott Laboratories Inc.’s legal regulatory practice, sings Cooper’s praises as well: "Rich is bright and creative, he has a broad base of knowledge, and his advice is balanced and credible. This combination of qualities makes him one of the most effective attorneys I’ve ever worked with."

Perhaps the biggest victory of Cooper’s career was also one of the biggest of all food-and-drug cases: the FDA tobacco litigation. Under Commissioner David Kessler, the agency moved to assert jurisdiction over tobacco products. Six leading tobacco companies filed suit in North Carolina federal court in 1996, calling the move by the FDA an unlawful effort to extend its regulatory reach and usurp the legislative authority of Congress.

In 1999, Cooper, who represented the RJ Reynolds Tobacco Co., argued the case before the Supreme Court. In March 2000, the Court by a 5-4 vote affirmed the decision of the U.S. Court of Appeals for the 4th Circuit that the FDA lacked jurisdiction under the Federal Food, Drug, and Cosmetic Act to regulate tobacco products.

"The position Reynolds took was consistent with the position the agency had historically taken," says Cooper, who calls the high court’s opinion "a correct decision."

A Rhodes Scholar, Cooper earned his J.D. from Harvard Law School in 1969. He clerked for Supreme Court Justice William Brennan Jr. Then, because the Peace Corps didn’t take lawyers ("quite sensibly," says Cooper), he signed

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up for a two-year stint in Uganda with the International Legal Center in late 1970.

But in 1971 Idi Amin seized power in Uganda, and Cooper found himself unexpectedly back in the United States that September. He turned to private practice, joining D.C.'s Williams & Connolly, where he made partner in 1976.

In 1977, Cooper took a job in the Carter administration, working under James Schlesinger in the White House Office of Energy Policy and Planning. Within the year, he had moved on to the FDA, where he served as chief counsel until 1979.

It was, he recalls, "a very rapid education in food-and-drug law." On his watch, Cooper says, the FDA essentially "created the modern market for generic drugs" with the development of the Orange Book, which lists brand-name and generic versions of drugs.

Cooper rejoined Williams & Connolly in 1980.
Richard Frank

Jenna Greene

09-19-2005

Among food lawyers, Richard Frank holds a place at the top of the pyramid.

A partner in Olsson, Frank and Weeda, he makes the case for a wide range of food producers, including PepsiCo Inc. subsidiaries Quaker Oats and Tropicana and trade groups such as the National Confectioners Association.

Lawrence Graham, president of the candy-makers organization, describes Frank as "extremely knowledgeable about food law, the history behind the laws and regulations, and how companies can deal with and anticipate changes."

Graham adds that Frank, who serves as the group's general counsel, has proved to be "a great help with strategy and with crisis situations."

Frank, 54, says he sees himself as "a choreographer." He explains: "There isn't just one way to address an issue. I try to bring to bear what Washington offers to move a matter for a client." This might include litigation, lobbying, or reaching out to consumer groups and the press.

This multidisciplinary approach was on display in a high-profile win in a dispute over the word "fresh." Frank's clients — several California tomato processors and an orange-juice maker he declines to identify — objected to the use of the word on labels for Ragu Foods' Fresh Italian pasta sauce and the Procter & Gamble Co.'s Citrus Hill Fresh Choice orange juice. Both products, Frank argued, could not be considered fresh, since they were made from concentrated tomato paste or concentrated orange juice.

The Food and Drug Administration "had not gone after labeling in 30 years. They didn't have the resources," Frank recalls. "So how do you get the FDA to actually do something?"

His solution: Partner with consumer groups, state attorneys general, and the media, and "keep hammering." In 1991 the FDA cracked down, even ordering U.S. marshals to seize a shipment of improperly labeled Citrus Hill Juice.

In another food-labeling victory, Frank represented the National Turkey Federation in a fight against the pork industry — first before the U.S. Department of Agriculture, then in federal courts — over the right to use the term "turkey ham" for a cured-turkey-thigh product.

He also helped the National Frozen Pizza Association (and continues to serve as the group's general counsel) in its efforts to prevent mandatory labeling of pizza made with nondairy cheese.

And recently, OmegaTech (now part of the Martek Biosciences Corp.) relied on him to get nutrient content claims approved by the FDA for the omega-3 fatty acids DHA and EPA.

Frank also chairs the nonprofit Food Institute, which provides information to the food industry.

But food isn't Frank's only business. He's currently pushing the FDA to change the rules for what he calls the "mouse type" that accompanies drug ads in magazines and other print publications. "No one reads it," he says. "And if they did, would they understand it? No."

So, Frank says, "we're trying to get the FDA to rationalize" this requirement. His idea: a "drug-facts" box, similar to the nutrition-facts box required for food products.
In this effort he's representing Catalina Health Resource, which works with drug companies and retail pharmacies to provide patients with information about their conditions and medicines. They're working in partnership with the National Consumers League on the issue.

Craig Scott, president of Catalina, calls Frank "a very strong partner to our business for more than 10 years" and "a real consigliere." Scott adds, "He's not only a very determined, dogged, and creative lawyer, but he's also a good businessperson."

Frank earned his J.D. from the University of Michigan in 1976. He joined then-Collier, Shannon, Rill & Edwards before striking out with partner Philip Olsson in 1979 to form two-lawyer Olsson & Frank. (David Weeda, who died in 2001, became a name partner in 1987.) Frank has served as managing partner of the now-30-lawyer food-and-drug firm since the beginning.

He is also the founder of the 10K race Lawyers Have Heart, now in its 15th year. (Legal Times has been a race sponsor.) A longtime runner, Frank says he wanted to do something to help improve the public image of lawyers. His father had heart disease, and Frank saw the race as "a double good" — a way to raise money for the American Heart Association and to "show that the Washington legal community has some heart."
Mark Heller

Jenna Greene

09-19-2005

From hair removal lasers to spinal implants to heart valves, Mark Heller knows the law on medical devices.

The chair of Wilmer Cutler Pickering Hale and Dorr’s Food and Drug Administration department, Heller, 58, is a veteran of both the FDA and the Federal Trade Commission. While in government, he played a key role in writing the landmark Safe Medical Devices Act of 1990. Today, he represents a broad range of medical device makers on all aspects of FDA product approval and compliance. He’s even written the book on it: Thompson Publishing’s Guide to Medical Device Regulation.

Joseph Gulfo, president and CEO of Electro-Optical Sciences Inc., says he turns to Heller for his “intellectual horsepower” and his reputation as “someone the agency trusts.”

Last year, Heller helped Electro-Optical swiftly secure a protocol agreement with the FDA for a clinical trial of MelaFind, a diagnostic system for the early detection of melanoma. "He gave us credibility and got us a very well-considered review by the agency," says Gulfo, who also praises Heller for his "phenomenal job of working with my experts."

Getting the green light from the FDA is a Heller specialty. In 2004, he helped Philips Medical Systems obtain agency clearance for its prescription HeartStart Home Defibrillator, which is used to treat sudden cardiac arrest. He then worked with the company in early 2005 to get the FDA’s OK for the first over-the-counter defibrillator, intended for use in homes, businesses, schools, and other public institutions. Heller describes the work as “a particularly exciting public-health-focused project.”

Heller has also represented KaVo Dental GmbH (now owned by the Danaher Corp.) in obtaining a risk-based class II classification for a noninvasive cavity-detecting device. Thus, the company could sell the product without first having to meet the FDA’s burdensome pre-market approval requirements.

"He’s a brilliant guy," declares Vivian Pratt, general counsel of Draeger Medical Inc., which makes anesthesia systems and other medical devices. "Anyone can give a focused, specific answer, but he looks at the broader implications for the product and the business."

Over the past 10 years, Pratt says, she has turned to Heller for assistance on device and drug matters ranging from interpretation of detailed requirements of the Federal Food, Drug, and Cosmetic Act to strategic advice on FDA compliance and product approval.

Heller’s practice has a significant public policy component as well. In recent years, he has registered as a lobbyist for such companies as Hillenbrand Industries, Cook Group Inc., and Fujifilm Medical Systems USA Inc.

Representing the Advanced Medical Technology Association (Advamed), Heller helped draft several provisions of the Food and Drug Administration Modernization Act of 1997. The law, says Heller, "streamlined pre-market clearance and put into place risk-based classifications." He also represented Advamed in connection with the Medical Device User Fee and Modernization Act of 2002.

Heller is a 1973 graduate of the University of Wisconsin Law School. He joined the FTC in the Bureau of Consumer Protection’s national advertising division, where virtually all his work concerned the food and drug industry. In 1981, Heller moved to the FDA as associate chief counsel for enforcement, and in 1984, he was named associate chief counsel for medical devices.
Highlights of his FDA tenure include successfully litigating in Michigan federal court in 1986 against the Stryker Corp. over a shoulder prosthesis marketed without appropriate clearance. In 1991, he won a case involving synthetic, absorbable sutures against Johnson & Johnson subsidiary Ethicon Inc. in D.C. federal court. That case, says Heller, "helped clarify FDA reclassification standards."

While officially at the FDA, Heller was also detailed to the Senate Committee on Labor and Human Resources to advise the chairman at the time, Sen. Edward Kennedy (D-Mass.). Heller's job: helping to draft the Safe Medical Devices Act.

"It was an absolutely wonderful experience," remembers Heller. "One real thrill in doing legislative work is that it allows you to participate in and witness the evolution of a body of law."

In 1991, Heller joined Patton, Boggs & Blow as a partner. Six years later, he moved to the D.C. office of Hale and Dorr, now part of Wilmer Cutler Pickering Hale and Dorr.
Peter Barton Hutt

Jenna Greene

09-19-2005

Peter Barton Hutt has done it all.

Food, drugs, cosmetics, medical devices, biotechnology — Hutt is renowned for the breadth and depth of his expertise in virtually every area of food-and-drug law. Indeed, Hutt, 70, is viewed by many as the dean of the food-and-drug bar.

"his level of experience and expertise is unsurpassed," says Martin Teicher, vice president and assistant general counsel of Pfizer Inc. and general counsel of Pfizer Consumer Health Care. "He's a role model for any new lawyer entering the practice."

Praising Hutt's vast knowledge of food-and-drug law, Teicher notes, "It's more than an ability to rattle off rules and regulations. It's his understanding of what the laws are intended to accomplish that is a priceless quality in a lawyer."

Over the course of his career, Hutt, now senior counsel at Covington & Burling, has served as chief counsel of the Food and Drug Administration; represented the largest food, drug, and cosmetic companies and trade associations; and testified before Congress dozens of times. He's also had a hand in virtually all the major food-and-drug laws passed in the past 35 years.

The son of a retail-dairy owner in Buffalo, N.Y., Hutt has had a keen interest in food issues since boyhood. After earning an LL.B. from Harvard Law School in 1959, he was awarded a one-year fellowship by the Food Law Institute to New York University, where he received an LL.M. in food-and-drug law in 1960.

That spring, Hutt literally knocked on the door of Covington & Burling to apply for a job, drawn by the D.C. firm's well-established food-and-drug practice. He was hired, and in 1968 he made partner.

Also in 1968, Hutt argued Powell v. State of Texas pro bono before the U.S. Supreme Court. At issue: whether it was cruel and unusual punishment to put an alcoholic in jail for public intoxication.

"I lost the case but won the law," says Hutt, who went on to draft legislation that created the National Institute on Alcohol Abuse and Alcoholism in 1970. For those efforts, Hutt was elected to the Institute of Medicine of the National Academy of Sciences, where he remains the only lawyer to attain membership based on his work in private practice.

As chief counsel of the FDA from 1971 to 1975, Hutt presided over a fundamental shift in the agency's legal mission. He describes the change as turning "a classic law enforcement agency" into "a modern administrative law agency that gets things done through administrative enforcement, informal compliance activities, and product review and approval — not the courts." He adds, "It had to be done."

Hutt recalls working 16 hours a day, seven days a week, in the FDA's top legal post, but still calls it "the best job in Washington."

Nonetheless, by 1975, and with four children in private school, he says, "I felt I had done what I set out to do." So Hutt returned to Covington.

A significant part of his work since then has been representing major trade associations. He currently serves as outside counsel for the Cosmetic, Toiletry, and Fragrance Association; the Grocery Manufacturers of America; and
Large corporate clients include Pfizer; the Procter & Gamble Co., which he has represented since 1962; and Schering-Plough Corp. In 2002, Hutt represented Schering in reaching a consent decree with the FDA over the use of good manufacturing practices in two plants in New Jersey and one in Puerto Rico.

In recent years he has become deeply involved in the biotech field. He currently serves on the board of directors of seven biotech companies.

And for the past 12 years, Hutt has taught a wildly popular three-week food-and-drug-law class at Harvard. He is currently working on the third edition of *Food and Drug Law: Cases and Materials*, along with Covington colleagues Richard Merrill, a University of Virginia School of Law professor, and Lewis Grossman, an American University Washington College of Law professor.

"When I started out in the field in 1959 . . . it was not difficult to grasp all the FDA regulations," Hutt remembers. "Today it's a Sisyphean task. But I have to keep up because I teach the subject."

Not that he finds it a hardship. "I love it all," he says. "No one in the world has any more fun than I do every day."
Daniel Krakov
Jenna Greene
09-19-2005

Patton Boggs partner Daniel Krakov is known for his keen political instinct and deft touch in handling sensitive matters. Both on Capitol Hill and before food-and-drug regulators, Krakov, 42, makes the best case for the manufacturers of biomedical products, pharmaceuticals, and medical devices.

Pfizer Inc., a major client, turns to Krakov for assistance with issues such as drug safety and the Prescription Drug User Fee Act, which comes up for congressional renewal every five years. In an e-mail, Dolly Judge, senior director of federal relations for Pfizer, writes that Krakov is "invaluable as a consultant," and praises his "ability to leverage his grasp of complicated subject matter along with his political insights."

He uses "his knowledge of the law" and "his understanding of the political environment," Judge writes, "to expertly guide our strategic thinking."

Kracov's skills in the legislative arena were on clear display in his representation of Internet contact-lens retailer 1-800-Contacts. The company, he says, was being "thwarted" by the prescription system. To prevent their patients from ordering contact lenses from lower-cost suppliers, Krakov explains, optometrists were simply refusing to give patients copies of their prescriptions.

Hired as a lobbyist, Krakov helped bring about the passage of the Fairness to Contact Lens Consumers Act, which went into effect in 2004. The law requires that patients be given copies of their prescriptions.

Kracov also helped secure a legislative solution for chemical and biotechnology company Lonza Inc. with the passage of the Food Quality Protection Act of 1996. The matter was critical, says Joseph Robinson, Lonza's vice president of regulatory affairs, because an earlier law had changed the classification of some of the company's products, thereby transferring regulatory oversight from the Food and Drug Administration to the Environmental Protection Agency. The act returned jurisdiction to the FDA.

Lonza has turned to Krakov for assistance with a variety of regulatory matters for more than 10 years, Robinson says. He describes Krakov as "aggressive, but not in a negative sense," and praises his direct manner: "He won't just say what the client wants to hear. It's an open and honest discussion."

Kracov is currently advising Pain Therapeutics Inc. on FDA-related strategy as it seeks to win approval for a series of new products. Pain Therapeutics is using a controlled-release mechanism to create abuse-resistant forms of controlled substances such as OxyContin.

The company "is trying to use technology to make drugs safer," says Krakov. "There's a lot of interest in these products." Hence, he continues, they "should be accelerated to market."

Kracov is also counseling Bavarian Nordic A/S on its efforts to provide smallpox vaccines for the U.S. stockpile.

Hoffmann-LaRoche Inc. is a big client. Krakov advises the company on regulatory and policy matters, including issues related to an anti-viral medication used to treat avian flu. He also helped Roche manage congressional inquiries in 2002 into its acne drug Accutane amid allegations of associated suicide risk among adolescents.

In another highly sensitive case, Krakov represented Johns Hopkins University School of Medicine scientist Alkis Togias. A participant in Togias' medical study on asthma died in 2001 after inhaling an experimental chemical. The episode received widespread publicity and raised questions about whether more federal safeguards are needed to protect research subjects.

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"It was a real lesson in what can go wrong," observes Kracov. Johns Hopkins settled the case for an undisclosed sum, and federal regulators temporarily suspended all human experimentation at the school.

Kracov received his law degree from the University of Virginia in 1988. He had worked at Patton Boggs as a summer associate and joined the firm upon graduation. A partner since 1995, he is currently deputy director of Patton Boggs' public policy and regulatory department. Notable colleagues include Stuart Pape and Paul Rubin.

Food-and-drug work offers a "fascinating combination of law, policy, science, health care," says Kracov. "It hits a lot of different buttons in terms of my personal interests."
"If my practice has a theme," says Wiley Rein & Fielding partner Bert Rein, "it's the limits of government authority and the proper boundaries of power."

A key player in some of the highest-profile food-and-drug conflicts in recent years, Rein has a record of successfully fighting off attempts by the government to expand oversight of industry.

Notably, Rein, 64, represented Brown & Williamson (now part of R.J. Reynolds Tobacco Co.) in the long struggle against the Food and Drug Administration's bid to regulate tobacco products. In 2000 the Supreme Court rejected the FDA's claim of jurisdiction.

Rein was also lead counsel for the Washington Legal Foundation in a case addressing the applicability of the First Amendment to FDA regulation of prescription drug advertising. The final decision from the U.S. Court of Appeals for the D.C. Circuit in 2000 established the ground rules for disseminating information about "off-label" uses for prescription drugs — that is, uses not specifically approved by the FDA.

Two years later, Rein persuaded the D.C. federal trial court to set aside the FDA's effort to require drug makers to study their products' effect on children, even if the product is not explicitly marketed for children's use. (Congress subsequently established new guidelines for pediatric testing.) Rein's clients — the Association of American Physicians and Surgeons, the Competitive Enterprise Institute, and Consumer Alert — argued that the pediatric rule exceeded the FDA's statutory authority and that its promulgation was arbitrary and capricious.

"He's phenomenal," says Jeffrey Chasnow, senior corporate counsel at Pfizer Inc. "Bert has a unique mastery of FDA issues." Chasnow praises Rein's "very astute and very strategic judgment," as well as his ability to "come up with workable solutions that make sense."

Rein recently represented Pfizer in a case likely to have a major impact on competition between brand-name and generic drugs. In June the D.C. Circuit upheld a lower court decision that Pfizer could sell a generic version of its blockbuster drug Neurontin, which is used to treat epilepsy and to relieve pain.

When Teva Pharmaceutical Industries Ltd. secured the rights to market a generic version of Neurontin, Pfizer moved immediately to market its own "authorized generic." Teva filed suit, asking the FDA to stop Pfizer. Teva argued that the 180-day exclusivity period granted to the first generic marketer should also bar the brand-name maker from offering a generic version. The court said no — a decision that stands to undercut the profitability of generic-drug makers and reduce incentives to challenge drug patents.

"It's a major, major issue for the generic industry," says Rein, who expects that generic companies will lobby for a legislative fix in upcoming months.

On Oct. 5, Rein is scheduled to argue for Wyeth Pharmaceuticals, maker of the anti-nausea drug Phenergan, in a case before the Vermont Supreme Court. The company is appealing a $7.4 million jury verdict in favor of a woman who lost her arm to gangrene after receiving an injection of the drug in an artery.

The FDA permits administration of the drug in a vein as a last resort, and the drug label warns of the possibility of gangrene if an artery is hit instead. The question is whether Wyeth nonetheless should have barred intravenous use as too risky.

Rein is not exclusively a food-and-drug specialist; his practice also includes antitrust and other litigation work. To
"He has a breadth of experience, and the ability to remember cases and legal theories and make connections that are not immediately apparent," says Marjorie Powell, senior assistant general counsel for the Pharmaceutical Research and Manufacturers of America, which has turned to Rein for strategic advice for more than 10 years. "He can come up with a whole variety of potential options, and he has the ability to evaluate their likelihood of success."

Rein graduated from Harvard Law School in 1964. After a two-year stint in the U.S. Army, he clerked for Supreme Court Justice John Marshall Harlan and then joined the D.C. office of Kirkland & Ellis.

He moved to the State Department in 1969, rising to become deputy assistant secretary for economic and business affairs. Highlights of Rein's government service included negotiating the Intelsat satellite agreement with 70 countries.

In 1973, Rein rejoined Kirkland & Ellis, where he remained until 1983, when he and 36 other lawyers broke off to form Willey Rein & Fielding.
Peter Safir

Jenna Greene

09-19-2005

Peter Safir's client list is a veritable who's who of pharmaceutical companies. During the past year alone he has advised more than half of the world's top 15 drug-makers, including Pfizer Inc., Sanofi Aventis Pharmaceuticals Inc., Johnson & Johnson, Merck & Co. Inc., Astra Zeneca PLC, Hoffmann-LaRoche Inc., Eli Lilly & Co., and the Schering-Plough Corp.

A partner at Covington & Burling, Safir is best known for his work involving issues pertaining to drug advertising, intellectual property and marketing exclusivity, and manufacturing quality and product safety.

Sanofi General Counsel Joe Haggerty relies on Safir for his experience and expertise. "I know when I call Peter, I'll get someone who probably knows the answer already," says Haggerty.

Safir has advised Sanofi on regulatory and marketing matters related to Allegra, Arava, and Lovenox. "He is not hesitant to help you make very difficult decisions," Haggerty says. "He has incredible judgment in terms of helping us navigate through legal issues in ways that are most successful for the company."

Linda Friedman, general counsel at Astellas Pharma Inc., shares this view. "Not only is [Safir] a terrific attorney, with a wealth of experience behind him, but he understands the business," she writes in an e-mail. "As a result, his advice is practical and on point."

As the co-head of Covington's food and drug practice, Safir, 60, works with a cast of all-star attorneys, including senior counsel Peter Barton Hutt. Other notable colleagues include Ellen Flannery, Richard Kingham, Eugene Lambert, and Richard Merrill.

Much of Safir's work relates to the Hatch-Waxman Act of 1984, which addresses the interplay between drug patent rights and Food and Drug Administration rules and establishes a system to encourage the marketing of generic drugs.

For example, Safir recently represented Johnson & Johnson before the FDA and in federal court to extend its exclusive right to market the pain reliever Duragesic for children. Mylan Laboratories had challenged Johnson & Johnson's right to pediatric exclusivity, which is granted by the FDA as a reward for conducting drug studies in the pediatric population. In December 2004, the U.S. Court of Appeals for the D.C. Circuit ruled for Safir's client, extending Johnson & Johnson's patent for six months.

In 2003-04, Safir successfully represented Pfizer in similar litigation over pediatric exclusivity, this time for the anti-fungal drug Diflucan.

Safir enjoys handling such cases. "They involve fascinating legal issues," he says, "but are rapidly resolved by the courts" — typically in about six months, with virtually no discovery.

He also provides clients with more general advice on drug life-cycle management — that is, "what strategies are available during the life of the patent to protect from premature generic competition."

One of the industry's biggest ongoing debates, in which Safir has a hand, is whether there should be a legal mechanism to allow for generic versions of patented biologic drugs, such as gene-based and cellular medicines. These drugs are unusually complicated to make, Safir notes, and one concern of his clients is that their manufacturing data covered by trade secrets might be revealed by the FDA to competing generic-drug makers.

http://www.law.com/jsp/dc/PubArticleFriendlyDC.jsp?id=1126602312379
Product safety is another Safir specialty. Last month he was retained as counsel to the Guidant Corp.'s independent panel investigating the company's defective heart defibrillator devices.

His work in the area of drug marketing is largely confidential, Safir says. Generally, it includes reviewing advertising campaigns and promotional materials and conducting internal investigations of marketing practices.

In 2002, Safir advised the Pharmaceutical Research and Manufacturers of America in drafting an industry-wide marketing code. "It sets out the appropriate relationship between pharmaceutical companies and physicians regarding gifts, grants, the overall relationship," he explains.


His enthusiasm for his work is clear. "People care about what they eat, drink, and put in their bodies. It's important," he says. "You read about what you're working on every day in the paper."

http://www.law.com/jsp/dc/PubArticleFriendlyDC.jsp?id=1126602312379
William Schultz

Jenna Greene

09-19-2005

William Schultz believes in fighting the good fight.

From the start of his career at Public Citizen to his stints on Capitol Hill, at the Food and Drug Administration, and in the Department of Justice, Schultz, 57, has made serving the public's interest a touchstone of his work life.

Now a partner at Zuckerman Spaeder, he represents generic-drug makers and small biotechnology companies as well as state governments and nonprofit groups. "It's not a traditional food-and-drug practice," he notes.

For example, the Campaign for Tobacco-Free Kids turns to Schultz for lobbying and litigation advice. "There's no one like him," says William Corr, executive director of the campaign. "He has an integrity and dedication to law and public service, trying to move the law in the food-and-drug practice in a positive direction from a public-health standpoint."

Schultz represented the Elizabeth Glaser Pediatric AIDS Foundation and the American Academy of Pediatrics (as Intervenors) after the U.S. District Court for the District of Columbia in 2002 ruled that the FDA had exceeded its regulatory authority by requiring more research into the effects of various drugs on children. As the case proceeded on appeal, Schultz simultaneously lobbied for legislation. In 2003, Congress passed the Pediatric Research and Equity Act, which requires pediatric studies of certain drugs and biological products (the litigation was subsequently dropped).

More recently, Schultz was part of a team of lawyers representing the state of West Virginia in litigation against Purdue Pharma L.P. over the narcotic OxyContin. The state alleged that Purdue withheld information about the drug's addictiveness in an effort to boost sales. The case was settled for $10 million in December 2004.

Schultz is now counseling the state of Illinois on its 1-Save program, which facilitates the importation of less-expensive drugs from Canada and the United Kingdom into the United States.

Among his many generic-drug clients, Schultz counts the trade group Generic Pharmaceutical Association and the multinational Alpharma Inc. In recent months, he has represented Alpharma in high-profile cases involving 180-day exclusivity for the generics metformin and gabapentin, two big-selling drugs. Both cases were settled favorably after intense litigation.

Brendan Magrab, former vice president for intellectual property at Alpharma, praises Schultz for his "impeccable judgment," noting his success with "major FDA issues that were worth millions of dollars to the company."

Schultz received his J.D. from the University of Virginia in 1974. After a one-year clerkship with U.S. District Judge William Bryant of the District of Columbia, Schultz took a job with the Public Citizen Litigation Group.

The first case he was assigned — concerning liability limits for the nuclear power industry — wound up before the Supreme Court as Duke Power Co. v. Carolina Environmental Study Group (1978). At age 30, Schultz had his first high court argument. (He didn't win.)

He appeared before the justices again in Young v. Community Nutrition Institute (1986). The case challenged the FDA's decision to set limits on the food carcinogen aflatoxin without public notice and comment. In the end, his client won the case on remand before the U.S. Court of Appeals for the D.C. Circuit. Says Schultz: "It redefined when the FDA is required to issue regulations."

http://www.law.com/jsp/dc/PubArticleFriendlyDC.jsp?id=1126602312387
In 1990, Schultz took what he describes as "a great job" working for Rep. Henry Waxman (D-Calif.) as counsel to the House Commerce Subcommittee on Health and the Environment. During his five years on the Hill he worked on legislation such as the Safe Medical Devices Act, the Prescription Drug User Fee Act, and the Nutritional Labeling and Education Act.

In 1994, Schultz moved to the FDA as deputy commissioner for policy, a position in which he was involved in the agency's efforts to regulate tobacco. Other issues during his four years at the FDA included consumer labeling of over-the-counter drugs, food safety, and pediatric drug testing.

Next, he served as a deputy assistant attorney general in the Justice Department. Schultz supervised the Civil Division's appellate litigation as well as the department's lawsuit, still ongoing, against the tobacco industry for violations of the civil provisions of the Racketeer Influenced and Corrupt Organizations Act.

Schultz joined Zuckerman Spaeder in 2001 as the first food-and-drug specialist in its D.C. office.
When it comes to big problems — the really big problems — William Vodra is often the lawyer of choice.

Whether advising Pfizer Inc. on how to deal with the Bjork-Shiley heart valve defect or representing the American Red Cross over blood safety problems, the Arnold & Porter partner has a long record of managing crises.

"If the chips are really on the line and it's a situation where you've got to have the best... he's the person I call," says Steve Oldham, general counsel for the Roche Diagnostics Corp.

Vodra, 62, is now helping Roche respond to a warning letter from the Food and Drug Administration about kits used to test for sexually transmitted diseases.

Oldham describes Vodra as "someone who can really give you the big picture of what you're facing and practical advice for how to get to the other side." He also praises Vodra's ability to "relate his experience to your particular situation in a way management finds easy to accept. That makes my job a lot easier."

Lawrence Stein, general counsel at Wyeth Corp., points to Vodra's "encyclopedic knowledge of food and drug law." But, Stein adds, "he's not simply a narrow specialist. He has the ability to bring his experience and judgment to bear in contexts that are broader than a particular regulatory problem." Vodra is assisting Wyeth with regulatory issues and product liability litigation.

Pfizer is a longtime client. One of Vodra's early matters for the company involved the arthritis drug Feldene. In 1986, Public Citizen's Sidney Wolfe petitioned the FDA to ban Feldene as an "imminent hazard." Instead, says Vodra, the FDA issued "a total and complete bill of good health" for Feldene as compared with other arthritis drugs.

A few years later, Pfizer faced a more dire problem. Reports came out that the Bjork-Shiley heart valve, which had been implanted in more than 70,000 people, could break down. The result was usually fatal. The company's stock had dropped 15 percent, Public Citizen was calling for FDA action, litigation was pending, and a congressional hearing loomed ahead. So Pfizer turned to Vodra.

The 1989 hearing, Vodra recalls, "was a critical event." Also important was Pfizer's subsequent announcement that it would track down and directly notify patients who had received the valve. Vodra assisted in that effort, as well.

It was a delicate task, to say the least. "How do you tell people there's a problem with something implanted in their body?" says Vodra. And while it was likely the recipients would die if the valve broke, he asserts, "it was even more risky to have open-heart surgery to remove it."

The American Red Cross also faced a high-profile problem. The organization was under fire for dangerous blood handling practices at its regional blood banks. Vodra represented the Red Cross in negotiating a 1993 consent decree requiring better management of blood service operations and improved quality controls.

These days, Vodra also helps drug companies deal with the threat of criminal charges. As the pharmaceutical industry has come under increased scrutiny in recent years, he says, "the risk is substantial that any serious regulatory problem could evolve into a criminal investigation."

Vodra earned his law degree in 1968 from Columbia University School of Law and then joined the Cincinnati firm Taft, Stettinius & Hollister.

http://www.law.com/jsp/dc/PubArticleFriendlyDC.jsp?id=1126602312398
In 1971 he came to Washington to work in the Justice Department's Bureau of Narcotics & Dangerous Drugs (renamed the Drug Enforcement Administration in 1973). Vodra dealt with licensing, security, and record-keeping issues for legal narcotics. "It was the most sheer fun I've ever had in a job," he recalls.

Vodra moved to the FDA in 1974 and was promoted to associate chief counsel for drugs in 1975. He helped write regulations for good laboratory, manufacturing, and clinical practices, along with working on the development of the Orange Book, which lays out therapeutic equivalents between brand-name and generic drugs. And he successfully defended the agency's decision to ban the diabetes drug phenformin.

In 1979, Vodra left the government to join Arnold & Porter's Washington office. He made partner in 1983. Notable colleagues at the firm include Arthur Levine, who is known for his expertise in responding to the threat of FDA enforcement actions, and Donald Beers, who handles a wide variety of FDA issues.
Exhibit 2
Preparing For FDA Inspections

Wed Jun 13, 2001

An important aspect of running a successful pharmaceutical, medical device, cosmetic, or food company is preparing adequately for on-site inspections by the U.S. Food & Drug Administration (FDA).

Under the Federal Food, Drug, and Cosmetic Act (FFDCA), FDA has broad authority to inspect any facility that manufactures, processes, or holds for introduction into interstate commerce foods, drugs, medical devices, or cosmetics. FDA agents are authorized to enter, without a warrant, any such facility provided that such entry falls within reasonable limits, and is conducted in a reasonable manner. FDA agents are further authorized to inspect all pertinent equipment, finished and unfinished materials, containers, and labeling therein. With respect to any establishment in which prescription drugs or restricted medical devices are manufactured or held, inspection shall extend to "all things" therein, including records, files, papers, processes, controls, and facilities pertaining to whether such articles have been adulterated or misbranded.

Inspections conducted prior to approval of a company's new drug or medical device are done primarily to confirm that the new drug or medical device can be manufactured safely and effectively. The results of such inspections are significant because they have the potential to deter the Agency's final product approval decision. Among other objectives, FDA conducts pre-approval inspections in order to verify the accuracy and completeness of the manufacturing-related information submitted in the New Drug Application (NDA) or pertinent medical device application (i.e., Pre-Market Approval (PMA)); evaluate the manufacturing controls for the pre-approval batches upon which information provided to the Agency is based; evaluate the manufacturer's compliance with Current Good Manufacturing Practices (CGMPs) as well as manufacturing-related commitments made in the NDA or PMA.

Because a great many inspections by FDA are unannounced, adequate preparation is key. To start this process, we have prepared the following checklist that pharmaceutical, medical device, cosmetic, and food companies should be prepared to address in the event of an inspection by FDA. Although this checklist generally covers the lifecycle of an inspection from start to finish, it is by no means exhaustive nor should it be interpreted to substitute the place of FDA legal counsel.

1. At the outset, the inspector should properly identify himself/herself and present written notice of inspection (Form FD-482) to the owner, operator or agent in charge.

2. The company should designate a person to receive and accompany the inspector. The designated person should be familiar with all aspects of company operating procedures, especially quality control procedures so he/she will be able to readily supply answers to any questions brought up by the inspector.

3. Prior to the start of the inspection, the designated person should ask the inspector why he/she is there and attempt to determine what he/she intends to review. This is also an appropriate time to inform the inspector of any company policies that will control the inspection.

4. During the inspection, it is imperative that the company protect its legal rights and not waive any privileges. A few basic tips on this include the following: Accompany the inspector at all times; advise the inspector that any questions or requests for data be directed only to the designated representative; keep a detailed record of everything the inspector says or does; finally, do not sign or initial affidavits or other documents.

5. FDA often asserts that it has the right to take photographs. Most companies do not permit photographs because the matter has not been judicially settled.

6. In considering whether to refuse a specific request from the inspector, the company may be protecting its legal rights appropriately. On the other hand, there is a risk that the company's refusal may be incorrect, thereby providing a basis for enforcement action or other penalties. Accordingly, the company may wish to consult legal counsel before providing, or refusing to provide, requested information.

7. Inspectors do not have authority to access personnel data (other than qualifications), sales, prices, and financial data (other than shipment data). If there is uncertainty as to whether the inspector has the right to review certain records, legal counsel should be consulted immediately.

8. At the completion of the inspection, the FDA inspector will meet with the "owner, operator or agent in charge." At this time, the FDA inspector provides an FDA form entitled Inspectional Observations (Form FD-483), listing observations the inspector believes are violations. (If the inspector observes no
violations, no FD-483 is issued.) This is the best time to discuss the list of observations with the inspector.

9. Promptly after the inspection has been completed, appropriate company personnel should meet to discuss the inspection. Legal counsel also should be consulted. At this time, a determination can be made as to whether a written response to the observations would be productive.

10. After the inspection, the inspector returns to his office and, over the next several days or perhaps weeks, prepares a detailed Establishment Inspection Report (EIR). The EIR becomes FDA's primary record of the inspection and is reviewed by FDA compliance officers. This EIR is available only when FDA has closed its file on the inspection.

11. If FDA concludes that an inspection has revealed significant violations, the Agency may initiate regulatory action such as seizure, injunction, detention, request for recall, etc.

-- Donald E. Segal

Footnotes

1 21 U.S.C. § 374(a)(1) (FFDCA § 704(a)(1)) ("Factory Inspection").

2 Id.

3 Id.

4 Id.

For additional information regarding these and other FDA-related matters, please contact Donald E. Segal at (202) 452-7959 or segalde@bipc.com.
Exhibit 3
December 8, 2003


The President signed into law today the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (the “Act”), which includes significant amendments to the statutory provisions governing the process for generic drug approvals.¹

These amendments to the Hatch-Waxman Act affect the availability of 30-month stays, 180-day exclusivity, and several other aspects of the generic drug approval process. Each provision is summarized in turn below.

I. 30-Month Stay

Multiple 30-Month Stays. Under the Hatch-Waxman Act, when an ANDA or 505(b)(2) application is filed with a paragraph IV certification challenging a listed patent in a referenced NDA, and the patent owner or NDA holder brings a patent infringement suit within 45 days of receipt of notice of the paragraph IV certification, FDA is prohibited from approving the ANDA or 505(b)(2) application for a period of 30 months, subject to action by the court.²

Under prior law, multiple 30-month stays could apply to a given ANDA or 505(b)(2) application. For example, if an ANDA was filed with a paragraph IV certification to a listed patent for an

¹ The Hatch-Waxman provisions are included in Title XI of the Act, which can be found as passed by the Congress at http://waysandmeans.house.gov/media/pdf/hr1/hr1-conflegtext.pdf. H.R.1, Title XI, reported in House Conf. Report 108-391 (Nov. 21, 2003). All citations to the legislation will be to the text of the bill as reported in the House Conference Report.

² FDCA § 505(c)(3)(C); § 505(j)(5)(B)(iii).
Covington & Burling

NDA, and the NDA holder brought a timely infringement action, a 30-month stay would arise.

If a new patent was subsequently issued by the Patent and Trademark Office and listed by the
NDA holder, then the ANDA applicant would have to make a certification to the newly issued
patent. If the ANDA applicant made a paragraph IV certification to the new patent, and the
NDA holder brought a timely suit based on the new paragraph IV certification, a subsequent 30-
month stay would arise.

The Act prevents multiple 30-month stays from arising in this manner by

providing that only patents filed with FDA before an ANDA or 505(b)(2) application is

submitted are eligible for a 30-month stay.\(^3\) Thus, when an ANDA or 505(b)(2) application is

submitted with a paragraph IV certification and the NDA holder or patent owner brings a timely

suit, a 30-month stay will arise. If a new patent subsequently issues and is listed, the ANDA or

505(b)(2) applicant must make a certification to that patent, and provide notice to the NDA

holder and patent owner if it is a paragraph IV certification, but there will be no 30-month stay

based on the new patent.\(^4\) This is the "centerpiece" of the Hatch-Waxman section of the Act.\(^5\)

The Act is similar in effect to the new regulations FDA issued on June 18, 2003,

which also sought to provide for only one 30-month stay for a given ANDA or 505(b)(2)

\(^3\) Title XI § 1101(a)(2) (amending FDCA § 505(j)(5)(B)(iii)); § 1101(b)(2) (amending FDCA

§ 505(c)(3)(C)).

\(^4\) Note that multiple 30-month stays can still arise if an ANDA or 505(b)(2) applicant makes one

paragraph IV certification at the time of filing giving rise to a 30-month stay, and then later

amends its application to make a new paragraph IV certification to a patent that was listed before

the application went in. This would occur where the ANDA or 505(b)(2) applicant makes a

paragraph III certification to a patent initially, and then later decides to convert that certification

to a paragraph IV certification, which could lead to a subsequent 30-month stay.

application. However, the Act and the FDA regulations work in a somewhat different manner. Under the FDA regulations, which became effective August 18, 2003, an ANDA or 505(b)(2) applicant is not required to give notice when amending an application to include a paragraph IV certification if the application already contains a prior paragraph IV certification. Thus, for example, when a new patent is listed, an amendment to certify to that patent does not trigger a notice requirement and cannot lead to a 30-month stay. Unlike FDA’s new rule, the Act requires that an ANDA or 505(b)(2) applicant provide notice of all paragraph IV certifications for patents listed in the Orange Book, “regardless of whether the applicant has already given notice with respect to another such certification contained in the application or in an amendment or supplement to the application.” However, paragraph IV certifications to patents listed after submission of the ANDA or 505(b)(2) application cannot trigger 30-month stays.

The Act supersedes these provisions of the FDA regulations, and the approach taken by the Act is helpful in at least two significant respects. First, it provides for notice to innovators of all patent challenges in an ANDA or 505(b)(2) application, even if the patent challenge cannot lead to a 30-month stay. Second, the Act is less subject to potential gamesmanship by ANDA and 505(b)(2) applicants than the FDA regulations.

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7 21 C.F.R. § 314.95(a)(3); 68 Fed. Reg. at 36678.
8 Title XI § 1101(a) (amending FDCA § 505(j)(B)); § 1101(b) (amending FDCA § 505(b)(3)).
9 Under FDA’s regulations, a generic applicant could use amended patent certifications to deprive innovators of a meaningful opportunity to trigger even one 30-month stay. In particular, an ANDA or 505(b)(2) applicant could file a paragraph IV certification in an original application to a selected patent, along with paragraph III certifications to other listed patents, and later amend the paragraph III certifications to paragraph IV certifications. The amended patent certifications would not trigger a notice requirement, and could not lead to a 30-month stay, because the amendments would be made to an application that already included a prior paragraph (continued...)

- 3 -
Timing of Notice. The legislation adds a requirement that notice of a paragraph IV certification must be provided to the NDA holder and patent owner not later than 20 days after FDA informs the applicant that the ANDA or 505(b)(2) application with the paragraph IV certification has been filed by the Agency. For paragraph IV certifications made in an amendment or supplement, notice must be provided when the applicant submits the amendment or supplement. Prior law contained no specific timing requirements for notice of a paragraph IV certification.

Amendments and Supplements. The Act provides that ANDA and 505(b)(2) applicants may not amend or supplement an application to refer to a different listed drug than the one identified in the original application. An amendment or supplement may be used to seek approval of a different strength, however, and the Act directs FDA to issue guidance on the meaning of “listed drug” for purposes of this provision within 60 days.

This provision on amendments and supplements is important for ensuring that ANDA and 505(b)(2) applicants do not attempt to use an amendment or supplement to evade the

IV certification. If the single patent challenged by the ANDA or 505(b)(2) applicant was a narrow patent on which the NDA holder or patent owner could not reasonably bring suit, the ability to obtain even one 30-month stay would effectively be lost. The Act does not permit this type of gamesmanship, because the notice and stay provisions apply in full to all of the patents listed at the time an ANDA or 505(b)(2) application is filed, whether a paragraph IV certification to those patents is made in the initial filing of the ANDA or 505(b)(2) application or in an amendment.

10 Title XI § 1101(a)(1)(A) (amending FDCA § 505(j)(2)(B)(ii)); § 1101(b)(1)(A) (amending FDCA § 505(b)(3)(B)).
11 Id.
12 Id. at § 1101(a)(1)(B) (adding new FDCA § 505(j)(2)(D)); § 1101(b)(1)(B) (adding new FDCA § 505(b)(4)(A)).
13 Id. at § 1101(a)(1)(B) (adding new FDCA § 505(j)(2)(D)); § 1101(b)(1)(B)(ii) (adding new FDCA § 505(b)(4)).
14 Id. FDCA § 505(j)(2)(D).
30-month stay provisions. Take, for example, an innovator drug product approved in both an immediate release and extended release formulation, with at least some different patents covering each product. Without the provision on amendments and supplements included in the Act, an applicant could obtain approval of an ANDA for the immediate release formulation, and then try to supplement the ANDA to obtain approval of the extended release formulation of the drug without having to face any 30-month stay on the extended release patents. This would arise because the Act provides that a 30-month stay can only be triggered based on patents listed before an ANDA is filed, and the original ANDA here would have been filed before there even was an extended release product, with that longstanding ANDA being amended to obtain approval of a new generic extended release formulation.

The Act prevents this type of bundling tactic by prohibiting an ANDA amendment or supplement from being used for a different reference listed drug such as an extended release formulation. This provision tracks existing FDA policy and codifies it in statute.

Termination of 30-Month Stays. The Act provides that entry of a district court decision holding that a patent is invalid or not infringed (including a settlement order or consent decree entered by the court stating that the patent is invalid or not infringed), will terminate a 30-month stay.\textsuperscript{15} If the district court holds that the patent has been infringed, the 30-month stay will terminate upon a decision of the court of appeals that the patent is invalid or not infringed (including an appropriate settlement order or consent decree entered by the court).\textsuperscript{16} If a district


\textsuperscript{16} Id.
Covington & Burling

court decision holding the patent infringed is not appealed or is affirmed on appeal, then the
ANDA or 505(b)(2) application at issue will be approved based on the district court ruling in
accordance with the expiration date of the patent.\textsuperscript{17} These provisions are consistent with current
FDA policy as well as several recent judicial decisions.\textsuperscript{18}

\textbf{Effective Date.} The 30-month stay provisions of the legislation apply to any
patent submitted to FDA on or after August 18, 2003.\textsuperscript{19} This date corresponds with the effective
date of FDA's new regulations and is intended to avoid a "three-regime" system in which some
patents are subject to FDA's old regulations, some to FDA's new regulations, and others to the
new statute. Under the new legislation, patents will be subject either to FDA's old regulations
(which allow multiple 30-month stays) or the new statute (which does not). The other provisions
of the FDA regulations, such as those dealing with which patents may be listed in the Orange
Book, are not affected by the new law.

\textbf{II. 180-Day Exclusivity}

\textbf{Forfeiture of 180-Day Exclusivity.} The Hatch-Waxman Act provides the first
generic manufacturer to submit an ANDA containing a paragraph IV certification with a 180-day
period of market exclusivity during which subsequent ANDAs may not be approved.\textsuperscript{20} Under
prior law, this exclusivity period was triggered by the earlier of first commercial marketing of the
generic product, or a court decision holding that the patent at issue is either invalid or not

\textsuperscript{17} \textit{Id.}


\textsuperscript{19} Title XI § 1101(c)(3).

\textsuperscript{20} FDCA § 505(j)(5)(B)(iv).
infringed. The new legislation eliminates the court decision trigger, retains the first commercial marketing trigger, and provides for several “forfeiture events” -- events that will cause the first ANDA applicant to lose its 180-day exclusivity.

The most significant of these forfeiture events is the “failure to market” provision, which provides that 180-day exclusivity is lost if the first ANDA applicant fails to market the drug by the later of:

- The date that is 75 days after the ANDA is approved by FDA or 30 months after submission of the ANDA, whichever comes earlier.
- The date that is 75 days after any of the following has occurred with respect to each of the patents for which the first ANDA applicant submitted and “lawfully maintained” a paragraph IV certification to qualify for 180-day exclusivity:
  - an appellate court decision finding that the patent is invalid or not infringed (in an action involving the applicant or another applicant with tentative approval),
  - court entry of a settlement or consent decree that includes a finding that the patent is invalid or not infringed (in an action involving the applicant or another applicant with tentative approval);
  - the patent listing in the Orange Book is withdrawn.

Other forfeiture events include withdrawal of the ANDA, amendment or withdrawal of all paragraph IV certifications qualifying the applicant for exclusivity, failure to obtain tentative

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21 *Id.*

22 Title XI §§ 1102(a)(1)–(2) (amending FDCA § 505(j)(5)(B)(iv) and adding new FDCA § 505(j)(5)(D)). Under the Act, commercial marketing can be of the generic product under the ANDA, or commercial marketing of the reference listed drug by the ANDA applicant, for example, under a license obtained from the NDA holder as part of a settlement.

23 *Id.* at § 1102(a)(2) (adding new FDCA § 505(j)(5)(D)(i)(I)).
approval of the ANDA within 30 months, entry by the ANDA applicant into an anti-competitive agreement, and expiration of all patents subject to the paragraph IV certification.\textsuperscript{24}

These provisions are intended to prevent ANDA applicants from obtaining and holding 180-day exclusivity in a way that unduly delays approval of subsequent generics. The provisions are complex, but the core of provisions is the establishment of a 75-day forfeiture clock running from the date of ANDA approval or the date of a court finding of invalidity or non-infringement on the relevant patents, whichever is later. Failure to come to market before the 75-day clock runs forfeits the 180-day exclusivity.

One particular 180-day exclusivity “parking” problem is addressed by the provision in the Act that the 75-day forfeiture clock is tied only to paragraph IV certifications that are “lawfully maintained” by the ANDA applicant. This provision helps ensure that there is not an incentive for ANDA applicants to file premature and speculative paragraph IV certifications solely for the purposes of obtaining first-in-line status.

Take, for example, an NDA where there is one listed patent covering the basic active ingredient (compound) expiring in Year 10 and another listed patent covering the particular NDA formulation expiring in Year 20. Without the “lawfully maintained” provision, an ANDA applicant might have an incentive to file well in advance of Year 10 with paragraph IV certifications to both innovator patents (compound and formulation), even though the ANDA applicant feels there is only a real basis to challenge the formulation patent. If the ANDA applicant files early and prevails in patent infringement litigation on the formulation patent, but

\textsuperscript{24} Id. (adding new FDCA § 505(j)(5)(D)(i)(II)-(VI)).
loses on the compound patent, the applicant would still earn and retain 180-day exclusivity based on the formulation patent.

The forfeiture provisions in the Act would not effectively apply to the 180-day exclusivity in these circumstances if it were not for the “lawfully maintained” provisions. This is because the compound patent would remain listed and there would never be a court ruling or settlement finding that the compound patent is invalid or not infringed. The 75-day forfeiture clock would thus not start, because it generally starts from the later of ANDA approval (or 30 months from ANDA filing) and a patent ruling of invalidity or non-infringement (or delisting) for each patent that is the subject of the paragraph IV certification. The ANDA applicant would thus have a strong incentive to bring an extremely early patent challenge, given that it could hold any 180-day exclusivity it earns until after expiration of the compound patent.

The Act avoids this result by tying the 75-day forfeiture clock only to paragraph IV certifications that are “lawfully maintained.” In the above scenario, when the ANDA applicant loses in the infringement litigation on the compound patent, it would be required under FDA policy to convert its paragraph IV certification for that patent to a paragraph III certification. Thus, the only lawfully maintained paragraph IV certification would be the one based on the formulation patent. The 75-day forfeiture clock would start upon the court’s finding of invalidity or non-infringement on that patent (or some time thereafter upon ANDA approval or elapse of 30 months from ANDA filing), and the ANDA applicant would effectively lose its 180-day exclusivity because the valid compound patent would prevent final FDA approval and marketing. The final provisions of the law thus help ensure that 180-day exclusivity will not act as an incentive for ANDAs to initiate premature and inappropriate patent challenges.
Additional 180-Day Provisions. The new legislation codifies several current FDA policies regarding other aspects of 180-day exclusivity:

- Exclusivity will be determined on a drug-by-drug basis, rather than separately for each patent. Thus, 180-day exclusivity is earned by the first ANDA application containing a paragraph IV certification, even if some later ANDA applicant is the first to file a paragraph IV certification as to other listed patents.\(^{25}\)

- Exclusivity will be shared by all ANDAs with paragraph IV certifications filed on the same day that the first ANDA with a paragraph IV certification is filed, and will not go solely to the ANDA filed earliest on that day.\(^{26}\)

- There is no “rolling exclusivity” -- if exclusivity is forfeited by the first-to-file ANDA (or all first-to-file ANDAs if more than one are sharing the exclusivity), then no applicant will be entitled to exclusivity.\(^{27}\)

Effective Date. The new 180-day provisions apply to ANDAs filed after the effective date of the legislation, provided that no other ANDA containing a paragraph IV certification had been filed for the same reference listed drug prior to the effective date of the legislation.\(^{28}\) For ANDAs subject to the old law, the legislation provides that the “court decision” trigger for 180-day exclusivity is the decision of an appellate court.\(^{29}\) Cases had interpreted the triggering “court decision” in the prior legislative language as a district court decision,\(^{30}\) and this will no longer be the case for ANDAs subject to the old law.

\(^{25}\) Id. at § 1102(a)(1) (amending FDCA § 505(j)(5)(B)(iv)(II)(bb)).

\(^{26}\) Id.

\(^{27}\) Id. at § 1102(a)(2) (adding new FDCA § 505(j)(5)(D)(iii)).

\(^{28}\) Id. at § 1102(b)(1).

\(^{29}\) Id. at § 1102(b)(3).

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III. Declaratory Judgments

Under existing law, ANDA and 505(b)(2) applicants were prohibited from bringing a declaratory judgment action regarding any patent that was the subject of a paragraph IV certification during the 45-day period following notice of a paragraph IV certification.\textsuperscript{31} No provisions of the Hatch-Waxman Act affirmatively stated whether or when a declaratory judgment action could be brought, and courts established various rules based on the principle that there can only be jurisdiction over an action under the Constitution where there is a ripe “case or controversy.”\textsuperscript{32}

In contrast to existing law, the Act affirmatively authorizes ANDA and 505(b)(2) applicants to bring a declaratory judgment action if the NDA holder or patent owner has not brought a patent infringement suit within the 45-day period, and grants the courts jurisdiction over such declaratory judgment actions “to the extent consistent with the Constitution.”\textsuperscript{33} The accompanying Conference Report explains that “the conferees do not intend for the courts to modify their application of the requirements under Article III that a declaratory judgment plaintiff must, to the extent required by the Constitution, demonstrate a ‘reasonable apprehension’ of suit to establish jurisdiction.”\textsuperscript{34} Therefore, even though the statute provides for declaratory judgment suits by ANDA and 505(b)(2) applicants, there remains the issue of whether the courts will hold that there is jurisdiction over such suits under the Constitution.

\textsuperscript{31} FDCA §§ 505(c)(3); 505(j)(5)(B).

\textsuperscript{32} See, e.g., Societe de Conditionnement en Aluminiun v. Hunter Eng’g Co., 655 F.2d 938, 944 (9th Cir. 1981).

\textsuperscript{33} Title XI § 1101(a)(2)(C) (adding new FDCA § 505(j)(5)(C)); § 1101(b)(2)(D) (adding new FDCA § 505(c)(3)(D)). Parallel changes are also made in regard to the declaratory judgment statute, Title 35 § 271(e), see Title XI § 1101(d).

\textsuperscript{34} House Conf. Report 108-391 (Nov. 21, 2003) at 386.
particularly where NDA holders and patent owners have not taken actions to create a "reasonable apprehension" of enforcing the subject patent or patents.

As a precondition of filing a declaratory judgment action to establish non-infringement, the Act requires the ANDA or 505(b)(2) applicant to make relevant portions of its application available to NDA holders and patent owners on a confidential basis to evaluate whether there is infringement.\textsuperscript{35} The Act requires that this information be treated as if it were trade secret or confidential business information and subject to a protective order.\textsuperscript{36} This new requirement for confidential access to information does not apply in the case of an ANDA or 505(b)(2) application containing a paragraph IV certification based on an assertion of patent invalidity, as opposed to non-infringement, presumably because validity generally turns on information external to the ANDA or 505(b)(2) application.

IV. Reporting Agreements to FTC and DOJ

The Act requires certain settlement agreements between drug manufacturers to be reported to the Federal Trade Commission and the Justice Department.\textsuperscript{37} The following agreements must be submitted to the FTC and DOJ:

- An agreement between a generic drug applicant that has submitted an ANDA containing a paragraph IV certification and a brand name drug company that concerns: (i) the manufacture, marketing or sale of the reference listed drug; (ii) the manufacture, marketing or sale of the generic product; or (iii) 180-day exclusivity (either of the generic manufacturer that entered into the agreement or of another manufacturer);

\textsuperscript{35} Title XI § 1101(a)(2) (adding new FDCA § 505(j)(5)(C)(i)(III)); § 1101(b)(2)(D) (adding new FDCA § 505(c)(3)(D)(i)(III)).

\textsuperscript{36} Id.

\textsuperscript{37} Title XI § 1112.
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- An agreement between two generic applicants that have submitted ANDAs containing paragraph IV certifications if the agreement concerns either company’s 180-day exclusivity; and

- Any agreements entered into by the above parties that are “contingent upon, provide a contingent condition for, or are otherwise related to an agreement” listed above.\(^{38}\)

Any agreements required to be filed with the FTC and DOJ must be submitted within ten business days after the date the agreements are executed.\(^{39}\)

V. Additional Provisions

**Delisting Patents From the Orange Book.** The Act provides that in a patent infringement action brought by the NDA holder or patent owner, an ANDA or 505(b)(2) applicant may assert a counterclaim for the delisting of patent information for the NDA from FDA’s Orange Book on the grounds that a patent does not claim the approved drug or an approved method of using the drug. The Act explicitly states that it does not authorize the assertion of an independent claim for delisting other than as a counterclaim in patent infringement litigation.\(^{40}\)

**Bioequivalence.** The Act authorizes FDA to establish methods for determining bioequivalence for drugs that are not absorbed into the bloodstream.\(^{41}\) This essentially codifies

\(^{38}\) *Id.* at § 1112(a)–(b).

\(^{39}\) *Id.* at § 1113.

\(^{40}\) *See id.* These provisions are consistent with court decisions holding that challenges to Orange Book listings may be entertained only in the context of a properly filed patent infringement suit. *See, e.g., Mylan Pharmaceuticals, Inc. v. Thompson,* 268 F.3d 1323, 1332 (Fed. Cir. 2001); *Abbott Laboratories v. Novopharm Ltd.,* 104 F.3d 1305, 1309 (Fed. Cir. 1997).

\(^{41}\) *See id.* at § 1103 (amending FDCA § 505(j)(8)(A)).
existing FDA regulations, and the legislation explicitly states that the new law "does not alter the
standards for approval of [ANDAs]."\footnote{See id at § 1103(b).}

\textit{Treble Damages.} The Act omits a provision in an earlier Senate version of the
law that would have limited the availability of treble damages for NDA holders and patent
owners in cases where patent information is not listed in a timely manner and an infringement
suit is nonetheless brought for damages. Treble damages continue to be available for willful
infringement.

* * *

If you would like further information about the new legislation, or would like to
discuss the implications of the statute or other Hatch-Waxman issues for particular NDAs or
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Exhibit 4
It's the Law

By Jeffrey K. Shapiro, Esq. and Joseph A. Levitt, Esq.

Condition of Approval Studies: FDA Takes A New Look

Medical device companies spend considerable time and resources conducting clinical studies to demonstrate the "reasonable assurance of safety and effectiveness" that is needed to gain approval from the Food and Drug Administration (FDA) of a premarket approval application (PMA). But when FDA's Center for Devices and Radiological Health (CDRH) decides to approve the company's PMA, it often does so with "strings attached"—an additional clinical study referred to as a "condition of approval." In other words, the "reasonable assurance" already demonstrated is not unequivocal. FDA has identified additional questions that the agency feels need to be studied after marketing to provide continued assurance of safety and effectiveness.

In the past, these condition of approval or postapproval studies have neither been taken seriously by device companies nor rigorously monitored by CDRH. Indeed, faced with the imminence of the long sought after approval of their PMAs, few companies have been willing to address the need or appropriateness of such further studies. Nor has the agency monitored or tracked the conduct or results of such studies very closely, turning its priority attention instead to the next PMA and its associated set of premarket clinical studies.

All that is about to change—and change rapidly. In this post-Vioxx environment, where FDA is being criticized for devoting disproportionate attention to premarket approval issues at the expense of adequate postmarket safety monitoring, all parts of FDA (not just the Center for Drug Evaluation and Research) are evaluating how to recalibrate that balance. Within CDRH, these condition of approval studies have become a top priority in recent months, and the device industry has responded in a very constructively way to improve the quality and focus of postmarket research.

This article places the issue of condition of approval studies into proper context. First, it reviews the legal framework surrounding condition of approval studies. Next, it describes what CDRH is doing to increase its monitoring of them. Finally, it examines what the medical device industry is doing—and what a sponsor can do—to ensure that, finite research dollars are well-targeted and well-spent.

Legal Framework

Under section 515 of the Federal Food, Drug, and Cosmetic Act (FD&C Act), FDA may grant PMA approval only if a sponsor provides reasonable assurance that a class III device is safe and effective for its intended use. That requirement appears to contemplate that all necessary evidence of safety and effectiveness will be provided prior to approval. Nonetheless, it is recognized that there are limitations to how much data companies can reasonably be expected to collect prior to marketing. Thus, although not expressly provided for in the statute, FDA's PMA regulation authorizes the imposition of condition of approval study requirements, under which a sponsor continues to obtain safety or effectiveness data after approval. Specifically, FDA may require:

Continuing evaluation and periodic reporting on the safety, effectiveness, and reliability of the device for its intended use. FDA will state in the PMA approval order the reason or purpose for such requirement and the number of patients to be evaluated and the reports required to be submitted.

The language of this regulation ("continuing evaluation") suggests that required studies will focus on long-term use of a device. This inference is reinforced by FDA's statement in the preamble:

FDA did not intend to suggest...that, as a condition to premarket approval, the agency would require that new clinical studies be performed on a device after a PMA is approved. FDA intended that for
certain devices a PMA applicant would be required to followup and report to FDA on a specified number of patients and devices after... approval.3

FDA’s apparent focus on long-term data reflects the agency’s legal rationale for requiring studies as a condition of approval. FDA believes it has authority under section 515 of the FD&C Act to require the submission of valid scientific evidence demonstrating the safety and effectiveness of a device’s long-term use.4 If such data are not available, FDA believes its only choice is to approve the PMA subject to a long-term study or to deny approval altogether until the long-term study is completed. The latter option would unnecessarily delay the benefits from a device that the agency may agree has been shown to be safe and effective for the short term. Accordingly, FDA has said it interprets section 515 to authorize studies as a condition of approval in order to assess the long-term safety and effectiveness of a device.5 Despite the stated legal rationale for condition of approval studies, FDA has sometimes imposed short-term study requirements to resolve issues that have arisen during PMA review. Few companies have challenged such requirements because FDA’s obvious alternative is to delay approval altogether until the new studies are conducted.

A PMA holder’s failure to conduct required postapproval studies, “constitutes a ground for withdrawal of approval of a PMA.”6 Of course, FDA also has the authority to withdraw the PMA if data from the studies show that the device is unsafe or ineffective or that there is a lack of reasonable assurance that it is safe or effective for long-term use.7

Increased FDA Attention

FDA has recently recognized that it has not given adequate attention to monitoring condition of approval studies.8 FDA’s most recent strategic plan spotlights an initiative to strengthen this area by improving the tracking of these studies, transferring the oversight function to organizational elements within CDRH that handle other postmarket surveillance, designing postmarket studies to address postmarket questions and following up with sponsors when requirements are not being met. Thus, CDRH Director Dan Schultz, MD, addressed the Orange County Regulatory Affairs Society (OCRA) annual meeting in June 2005 and reportedly stated that there is a new tracking system underway “so that we can be sure that when there are commitments made, we know what they are, when the reports are due and that we can communicate quickly and efficiently with sponsors to make sure that the reports come in on time.”8

The transfer of oversight to another part of CDRH is particularly noteworthy. Historically, because these studies originated with the center’s premarket offices (Office of Device Evaluation (ODE) or Office of In Vitro Diagnostic Evaluation and Safety (OIVD)) as part of the product’s PMA review, these same offices were charged with monitoring the postmarketing conduct of these studies and reviewing the studies’ results. The center recognized, however, that these same offices were under tight timeframes to meet the premarket performance goals associated with the Medical Device User Fee and Modernization Act (MDUFMA) and that a reassignment of responsibility within CDRH was appropriate.

Accordingly, Dr. Schultz decided to transfer the responsibility for monitoring these studies to the Office of Surveillance and Biometrics (OSB). This office has the other major postmarket product safety responsibilities, including the review of Medical Device Reports (MDRs) of patient injuries and product malfunctions, as well as postmarket surveillance studies that are mandated by the center when safety issues that warrant further study arise postmarketing. Within this framework, the logic behind this administrative move within CDRH is clear: place the center’s staff who oversee “postmarket” device safety on a daily basis in charge of all clinical studies that are designed to be conducted after marketing.9 The OSB Director, Susan Gardner, PhD, has made a series of presentations before CDRH advisory panels on how her office will approach this new function. Dr. Schultz noted at the OCRA meeting that FDA is developing new guidance on postapproval studies that it hopes to issue by the end of this summer.

Industry Response—Establish Principles

As it has become clear that FDA intends to improve tracking and enforcement of postapproval study requirements, the medical device industry has responded with
a series of recommendations as to how condition of approval studies could be made more valuable by devoting more attention “up front” to exactly what studies are warranted and under what clinical protocol. Specifically, in early February 2005, AdvaMed, the nation’s leading association of medical device manufacturers, submitted a document to CDRH entitled, “Principles of Condition of Approval Studies”.

These principles were developed by AdvaMed member companies and represented their best thinking on such issues as how to ensure that these studies are designed to meet specific objectives; that protocols for such studies are agreed upon between the agency and the sponsor; and that there are understood timeframes for the conduct of these studies. By emphasizing the development of the need for and character of such studies, and on the need for this to be a collaborative effort, the industry properly recognizes that more attention needs to be placed at the “front end” if the monitoring at the “back end” is to be meaningful.

What a Product Sponsor Can Do
One lesson here is that a company seeking PMA approval should carefully think through its position regarding the need for and/or scope of postapproval studies. Too many companies hope to get by without a requirement (or worse, fail to consider the issue) and then accede when FDA (or a panel member) raises the issue at the eleventh hour. While the desire to quickly remove a final obstacle to approval is understandable, companies need to weigh the short-term gain against the long-term consequences, because it is now likely that FDA will closely monitor and seriously enforce condition of approval study requirements.

If the device is to be used on a long-term basis, it is important to think through what type of study, if any, and what design would be appropriate. If the company’s device is not to be used on a long-term basis, there should be a very clear reason for FDA to impose this requirement and any such request should be closely scrutinized. In any case, it may be advisable to initiate a discussion with FDA earlier in the PMA process and to negotiate vigorously on this issue to ensure the need, scientific soundness and practical feasibility of any required study.

Conclusion
The recent attention by both FDA and the medical device industry to improve the design, conduct and monitoring of condition of approval studies is an example of the system righting itself. CDRH correctly recognized that, if it is going to insist upon postmarketing studies with any frequency, it had better institute a monitoring system upon which the public can depend. Simultaneously, the medical industry recognized that, if these studies are going to receive higher visibility, more attention ought to be given to ensuring the studies are worthwhile and well-designed and that the timetable for completion is reasonable. Moreover, the agency and industry appear to be working collaboratively on this endeavor, with the winner being the American public, which will now benefit from new technology that is studied more carefully than ever before.

NOTES
1. The Food and Drug Administration Modernization Act of 1997 (FDAMA) added section 506H to the FD&C Act, which imposes requirements when “[a] sponsor of a drug...has entered into an agreement with the Secretary to conduct a postmarketing study of the drug.” FD&C Act, § 506(h)(1).
   This provision suggests a congressional recognition that postmarketing studies are authorized under the FD&C Act in at least some circumstances.
2. 21 CFR § 814.82(a)(2).
3. 51 Federal Register 26364, 26359 (July 22, 1986).
4. 51 Federal Register at 26359.
5. Id.
6. Id.
7. 21 CFR § 814.82(c); see also id. § 814.46(a)(2).
8. Id. § 814.46(a)(1).
9. FDA conducted a review several years ago of condition of approval studies over a two-year period. The review findings were not publicly released. However, after public attention turned to postmarket product safety in the fall of 2004, CDRH cited the review as indicating that a significant percentage of postapproval studies (22%) did not have adequate follow-through. The device industry responded, very directly, that FDA got its facts wrong. AdvaMed contacted every one of its member companies cited in the study, and each company stated that it had followed through with the promised study (or had a valid reason not to do so agreed to by FDA). Faced with clear factual rebuttal, CDRH appropriately stopped referring to the 22% figure that had gained public attention.
10. Dickinson’s FDA Webview.
11. FDA has authority under MDUFMA to utilize user fee funds for monitoring condition of approval studies, regardless of which part of CDRH performs such monitoring.

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Exhibit 5
Commentary

Exploring other options

Part 2: Facilitating the FDA review process

Jeffrey N. Gibbs

The first installment of this article (IVD Technology, May 2005) explained how IVDs that have not undergone FDA review are proliferating. Even though such tests have not obtained FDA authorization or been cleared for the indications for which they are being used, laboratorians and clinicians need to be able to conduct and order them. Restricting labs to only FDA-cleared IVDs would have adverse medical consequences, particularly since home-brew tests are well entrenched in the clinical decision making process. Nevertheless, the healthcare system’s reliance on tests that have not been reviewed by the agency raises some pressing questions.

For example, would the systemic bypassing of FDA have a net positive or negative effect? If many new, sophisticated IVDs enter the marketplace via home-brews or other means and then never undergo FDA review, is that a cause for concern, and does anything need to be done? In other words, if the trend toward adopting non-FDA-approved tests accelerated, would that be a bad thing?

Moreover, what will the ultimate impact be for the IVD industry and innovation if this trend persists? AdvaMed (Washington, DC) has weighed in on this issue by arguing that IVD manufacturers are put at a significant competitive disadvantage because of the lower regulatory hurdles for home-brews, and that “the risks posed by lab-made tests that lack FDA oversight cannot be underestimated.”

On balance, the FDA review process, which includes careful examination of packaging inserts and product performance, probably does result in better clinical management. Congress certainly made that policy judgment by including IVDs within FDA’s jurisdiction. Given that submitting product applications to the agency is in the public’s interest, a key question, then, is what regulatory measures can be implemented to induce IVD manufacturers to seek FDA marketing authorization, rather than follow one of the alternative commercialization routes. The agency could take a number of concrete steps that would encourage more manufacturers to seek market access through the FDA review process.

Product Review Processes

For example, FDA could make the review process more predictable. IVD manufacturers would benefit by knowing early in the process whether their new products will be subject to review through the 510(k), premarket approval (PMA), or de novo process. Since predictability matters a great deal to manufacturers, uncertainty may deter those companies that cannot get a clear indication at an early stage of what the agency plans to do.

FDA generally appears to underestimate the costs and side effects of uncertainty in the review process. If IVD manufacturers find out their products are being reviewed differently than had been expected, they are more likely to pursue a non-FDA alternative the next time. Moreover, unexpected late changes in a new IVD’s regulatory status can have a ripple effect. IVD manufacturers share their regulatory concerns with other companies, which may then consider other market pathways for their products.

FDA also needs to recognize that PMAs are far more burdensome than 510(k)s for IVD manufacturers. Some agency officials appear to believe that as long as a manufacturer is conducting a PMA-caliber clinical study, the incremental requirements of the PMA process are negligible. However, PMAs are significantly longer, preapproval inspections are taxing and add uncertainty, user fees are much higher, and advisory panels, when necessary, not only cost time and money but also add unpredictability. Moreover, PMAs are even more burdensome once approval is secured (e.g., filing annual reports) and offer less flexibility in making labeling, product, and manufacturing changes. PMAs are much more costly and difficult than 510(k)
s. even when the clinical requirements are no greater.

A relatively new regulatory option is de novo review. This process allows FDA to clear new IVDs via a 510(k) even without a predicate device. De novo review can significantly facilitate market entry and reduce the post-approval workload that the PMA process engenders.

The Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD) has been receptive to de novo review by clearing more de novo applications than the rest of the Center for Devices and Radiological Health (CDRH) combined. Given the benefits of de novo review and the suitability of many new analytes to this process, OIVD should further expand its use. Moreover, OIVD should commit to the de novo process at early-stage meetings with IVD manufacturers. Earlier knowledge that this route is available can encourage manufacturers to pursue FDA marketing authorization. Conversely, uncertainty about the route of de novo review 510(k) (instead of PMA) can deter IVD manufacturers from going down the FDA approval pathway.

In fact, OIVD is willing to discuss regulatory pathways at early-stage meetings. The information that OIVD provides at this stage is valuable and helps IVD manufacturers formulate their plans for the review process. However, discussions do not guarantee predictability. Sometimes, a manufacturer is advised that a pathway is contingent upon the data, which offers little certainty. Occasionally, the pathway may be altered during the review process. While such situations are rare, they can add regulatory complexity and delay for affected companies.

Clinical Studies

The need for certainty also extends to the design of clinical studies to support a premarket submission. The FDA Modernization Act (FDAMA) gives manufacturers the right to ask the agency to agree formally to a protocol which will result in approval if followed. However, this congressionally bestowed provision has been used sparingly. FDA prefers informal understandings.

Although such understandings are often honored, that is not always the case. Knowing that FDA is likely to follow an informal agreement on the parameters of a clinical study (e.g., the number of subjects, endpoints, and data to be collected) may not provide an IVD manufacturer with a high enough level of confidence to justify a large investment in a study, particularly if other, more certain, commercialization options exist. In fact, manufacturers should be aware that an FDA regulation permits the agency to disown virtually any statement made by any of its employees.

While informal agreements are helpful, they do not provide assurances. This point was driven home at a non-IVD advisory panel in 2003. During the panel meeting, a company noted it had used a protocol that FDA had accepted. A division director repudiated those agreements, saying the sponsor should not have relied on the protocol:

Yes, I just want to comment, maybe just because I am from FDA, that it bothers me, the use of the terms “required” and “agreement,” since neither of them are really the case. We have guidances, and that means we provide our recommendations to sponsors, and we have discussions with them about what our best recommendations are about testing to address the issues in that application. But it is not requirements, and “agreement” has a specific meaning to us, where we have an agreement if they do this, that will get them approval.

Even though an OIVD official did not make this statement, it does reflect FDA’s strict legal interpretation that a nonstatutory agreement is not binding.

To its credit, OIVD has been receptive to pre-investigational device exemption (IDE) meetings to discuss proposed clinical studies. OIVD has encouraged IVD manufacturers to meet and discuss regulatory pathways and data requirements. OIVD is now conducting its own evaluation of the value of pre-IDE meetings. However, CDRH has been reluctant to enter into binding agreements, even though that procedure is specified in FDAMA. For companies and investors looking for a high degree of certainty, there can be a difference between a good-faith commitment and a statutorily defined agreement. While IVD manufacturers can and do rely on commitments given by OIVD during pre-IDE meetings, they are not legally binding. Manufacturers need to know that their data will lead to approval or clearance if the studies meet agreed-upon criteria.

IVD manufacturers that have encountered evolving requirements during a product review may look for alternatives that do not involve FDA when developing their next product. Similarly, altering the data requirements because of changed agency personnel can create difficulties for IVD product sponsors. A manufacturer that was advised that collecting data set X would be acceptable should be able to rely on that statement, even if a new reviewer or statistician joins the review team.

Conversely, real-time reviews can expedite approvals and clearances. Raising and resolving issues with an IVD manufacturer about its clinical study as they are identified can accelerate the review process and improve stakeholder satisfaction.

Having FDA ask questions that it should have asked earlier in the review process is another issue. It is frustrating for an IVD manufacturer to have its 510(k) undergo an extra review cycle because an FDA reviewer did not ask questions the first time. (Such inquiries are distinguished from raising questions about new information provided in the initial reply.) The loss of 90 days or more can be a heavy blow to a manufacturer, and receiving an avoidable not-substantially-equivalent letter because of an extra review cycle is costly. Given how rapidly technology changes, new IVDs can have a comparatively short commercial shelf life.
Data Requirements

FDA's data requirements need to be reassessed, particularly with respect to clinical utility. Obtaining clinical data is one of the biggest stumbling blocks to gaining FDA authorization for new IVDs. Data requirements should be limited to supporting the claims in the packaging inserts as written by the IVD manufacturers. Information regarding potential uses, as opposed to claimed uses, should not be required.  

FDAMA directed the agency to apply the least burdensome data requirements for medical devices. CDRH has also issued an implementing guidance. OIVD personnel have quoted this provision in discussions with the IVD industry. Nevertheless, the clinical data requirements that are actually imposed are not always consonant with the least burdensome directive.

One IVD industry proposal that would result in FDA oversight of an IVD's analytical performance but would not require clinical data in order to obtain marketing authorization has encountered a frosty reception. CDRH has been reluctant to accept the request to establish a new regulatory category called in vitro analytical tests (IVAT). Although last year David Fegel, MD, and Steve Gutman, MD, stated that FDA would "continue to consider the IVAT proposal," the agency so far has not been receptive. At the same time, Feigel and Gutman acknowledged the need to consider "new ways of reviewing IVDs based on a total product life cycle approach."

In response to comments on the IVAT proposal, FDA has stated that analytical performance as a basis for premarket clearance is common in cases in which the link between analytical and clinical results is well established. Analytical performance as a basis for clearance is already feasible under current FDA regulations and is being used. The recently cleared cystic fibrosis test apparently relied upon this type of data. However, when clinical use of a new IVD is not well linked to analytical performance, FDA's view is that current requirements would call for a clinical study. While FDA has noted its interest in novel review techniques as they might apply to both its least burdensome and critical path initiatives, the agency's view has been and remains that the safety and effectiveness of IVD devices relate to both analytical and clinical performance.

Greater reliance by FDA on design controls, manufacturing controls, and postmarket controls should enable the review of many applications with less up-front data. The agency can also use its flexible ability to impose special controls on Class II devices for accelerating the review and market introduction of new IVDs.

CDRH's recognition of the need to find new ways of conducting reviews is potentially promising. However, more-concrete actions are required. For IVD manufacturers that have developed novel products, imposing unnecessary clinical data requirements is a major deterrent to pursuing the FDA approval pathway. FDA should accompany its requests for more data with a reasoned explanation for why the data are needed, and should give the manufacturer a prompt, fair opportunity to respond. The agency should utilize alternative approaches, such as narrower labeling and the use of special controls for Class II devices, in lieu of more-robust labeling studies. The data requirements should be based on the intended use in the labeling, and not potential clinical applications outside the labeling. Risk-based approaches should be considered. As AdvaMed proposes in its comments on the critical path initiative, unnecessary barriers to obtaining clinical data (e.g., informed-consent requirements for anonymous banked specimens) should also be scrapped.

Other Regulatory Changes

A relatively minor change in policy may also make 510(k) more attractive. IVD manufacturers can now promote that they have obtained premarket approval. Still, the ability to publicize 510(k) clearance is circumscribed. FDA regulations prohibit manufacturers from creating "an impression of official approval of a device" because a 510(k) was obtained. Allowing IVD manufacturers to advertise that they have received FDA clearance could be an incentive by providing a marketing edge over products that cannot make that claim.

While the focus should be on carrots, the sticks cannot be ignored. For example, while research use only (RUO) products should not be promoted for diagnostic use, a number of IVD manufacturers still engage in that practice. The existence of RUO products directly competing with FDA-cleared devices can serve as a disincentive for going through FDA. If another manufacturer is able to sell unimpeded an unapproved RUO product for the same claims, 510(k) and PMA holders are apt to question the value of their own 510(k)s and PMAs. This is more likely to be the case when a competitive RUO product remains on the market even after FDA has been alerted. To the extent that unlawful diagnostics are aggressively promoted, it can discourage IVD manufacturers from making the investments necessary to obtain FDA approval or clearance.

Conclusion

Other steps can also be taken to facilitate the FDA review process and make it more attractive. This article is hardly an exhaustive list. For example, OIVD is looking at electronic submissions. OIVD has already taken many positive steps, such as holding pre-IDE meetings, providing rapid feedback via e-mail to facilitate communications, and showing flexibility, such as its use of the de novo process. However, it is important that FDA, the IVD industry, laboratories, and other stakeholders candidly critique the current review process and identify steps that will facilitate the product development, review, and approval processes for diagnostics. Clearer, more predictable, more transparent, and less regulatory pathways to market need to be available for IVD manufacturers that wish to introduce new types of diagnostic products. The atrophy of the statutory product development protocol mechanism illustrates what happens to a regulatory process when it becomes too costly, prolonged, cumbersome, and uncertain.
References


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Exhibit 6
Will Food Laws Be Uniform?

Sheila A. Millar, Attorney-at-Law, Keller & Heckman, Washington, DC

Apr 1, 2006 12:00 AM

Legal Briefs

On March 8, the US House of Representatives passed legislation that would preempt food safety and labeling laws. Federal preemption is a legal concept under which states may not enact regulations unless they are identical to federal law.

H.R. 4167, the National Uniformity in Food Act, is intended "to provide for uniform food safety warning notification requirements." If enacted, it would preempt the California Safe Drinking Water and Toxic Enforcement Act of 1986, better known as Proposition 65, which requires warning labels on substances known to the state to cause cancer or reproductive toxicity. The bill has been referred to the Senate, and opponents are gearing up to oppose its adoption.

Business supporters of H.R. 4167, however, say national uniformity is needed to provide certainty for both domestic and international providers of food and food packaging materials in today’s complex global economy.

The bill includes separate provisions on national uniformity for foods and for food safety warning notification requirements.

With respect to food safety warning requirements, the bill says no state may directly or indirectly establish or continue in effect any notification requirement for a food that provides for a warning concerning the safety of the food, or any component or package of the food, unless it is identical to the notification authority prescribed under the Act.

The definition of the term notification requirement includes any mandatory disclosure requirement through a label, labeling, poster, public notice, advertising, or other means of communication.

States may petition for an exemption or a national standard under the bill. If such a petition is filed within 180 days after enactment, the state notification requirement will remain in effect pending final action on a rulemaking in response to the petition.

In addition, the Act allows states to petition for an exemption if a requirement protects an important public interest that would otherwise be unprotected, would not cause the food to violate federal law, and would not unduly burden interstate commerce.

Specified time periods are provided, and expedited consideration is required if a petition involves a warning related to cancer or reproductive or birth defects, or is intended to allow parents to limit a child’s exposure to cancer-causing agents or reproductive or developmental toxins.

Finally, states may establish a requirement that would otherwise violate the measure through inconsistency with federal law if it is needed to address an imminent hazard to health likely to result in serious, adverse health consequences, subject to adherence to certain procedures.

The bill is under discussion at an unusual time, when some legislators that historically have supported states rights are being persuaded that national uniformity is needed, while others that historically have supported a strong federal role are concerned

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that the federal government is failing to regulate.

For the converting industry, the role of federal preemption will be of increasing importance, not just in connection with debates surrounding H.R. 4167 but in the field of environmental regulation as well.

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To read more of Sheila A. Millar’s Legal Briefs columns, visit our Legal Briefs Archives.

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Exhibit 7
Strategic Implications of FDA’s Proposed Safety Reporting Requirements

by Lawrence S. Ganslaw and Michele L. Vockrodt

On March 14, 2003, the Food and Drug Administration (FDA) issued a proposed rule to expand the requirements for pre- and postmarketing safety reporting for human drug and biological products, to “further worldwide consistency in the collection of safety information and submission of safety reports, increase the quality of safety reports, expedite FDA’s review of critical safety information, and enable the agency to protect and promote public health.” The strategic implications of the proposed rule concern the scope of the new reporting requirements, product liability, privacy law and enforcement implications, and effects on product lifecycle.

Scope of Reporting Requirements

Under the proposed rule, manufacturers’ safety reporting obligations would be increased both with respect to the types of events that must be reported and the information that must be submitted for each report.

The universe of events considered reportable would be expanded through changes in key definitions and the addition of new requirements. The proposed rule would replace the existing regulatory term “adverse drug experience” with “suspected adverse drug reaction” (SADR), which is defined as “a noxious and unintended response to any dose of a drug product for which there is a reasonable possibility that the product caused the response.” Importantly, the phrase “reasonable possibility” means that the relationship cannot be ruled out. Even if the event is considered only “remotely related” or “unlikely related” to the drug product, it would need to be reported. Unless it can be said with certainty that the adverse reaction was not caused by the drug product, it will be considered an SADR.

FDA also is proposing, for the first time, that actual and potential medication errors be reported. An actual medication error is defined as a medication error that involves an identifiable patient, whether or not the error was prevented prior to administration and whether or not the error resulted in an SADR (serious or nonserious). A potential medication error is a report or complaint concerning product name, labeling, or packaging that does not

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involve a patient. The new requirement for reporting medication errors—
together with the expanded definition of an SADR—would significantly
increase manufacturers' safety reporting obligations.

The proposed expansion in the
types of events to be reported would be
further magnified by the investigation
and documentation requirements for
each reportable event. The proposed
rule would necessitate that an "active
query" be performed upon receipt of
an SADR or medication error, which
requires direct verbal contact with the
initial reporter by a healthcare pro-
essional (i.e., physician, physician
assistant, pharmacist, dentist, nurse or
any other individual with some form of
healthcare training) representing the
manufacturer. For SADRs, the active
query would require, at a minimum, "a
focused line of questioning designed to
Notwithstanding the laudable
goals of the proposed rule, it is unclear
whether FDA will be able to manage
and make effective use of the information
generated by the expanded safety
reporting requirements. The Prescrip-
tion Drug User Fee Amendments of
2002 (PDUFA III) included an esti-
mated increase of $5.7 million for fiscal
year 2003 for expanded pre- and post-
approval safety reporting. In its PDUFA
III five-year plan, FDA indicated that it
expects to use this increase to provide
for 10 additional full-time employees
to enforce postmarketing adverse event
reporting regulations ($1.2 million),
and for upgrades to the adverse event
reporting system (e.g., electronic
reporting) ($4.5 million). 4 Even if FDA's
electronic adverse reporting system is
dramatically upgraded and the agency
has additional enforcement staff, it is
not clear that these increased resources
to the adverse event." Nevertheless,
product liability plaintiffs frequently
attempt, and often are permitted, to use
adverse event reports for a variety of
purposes, including:

- as evidence that a drug caused the
  reported adverse event;
- to prove the incidence in the gen-
  eral population of adverse events
  "similar" to those alleged;
- at the expert stage to overcome
  a plaintiff's burden to establish
  causation;
- at the trial on the merits, where
  voluminous reports are presented
  to persuade the jury that the drug
  caused the problem; and
- in the punitive damage stage, to
  demonstrate awareness of, and
  failure to address, drug problems.

FDA has proposed no changes to
the adverse event report disclaimer,
capture clinically relevant information
associated with the drug product ... and
the SADR, including, but not limited
to, information such as baseline data,
patient history, physical exam, diagnos-
tic results, and supportive lab results. 3

The proposed rule also would
require that a licensed physician be
responsible for the content and med-
cal interpretation of the safety reports
submitted to FDA. If a patient associ-
ated with a reportable event dies, the
manufacturer would need to submit a
copy of the autopsy report, if available,
or a death certificate. If the patient is
hospitalized, the hospital discharge
summary would need to be submitted,
if available. 4

are adequate to ensure that mean-
ful information is derived from, and
appropriate actions are taken based on,
the increased number of reports.

Product Liability
FDA's adverse event reporting
system database is publicly available
by quarterly subscription. Plaintiffs'
lawyers have been known to monitor
the system for potential product liability
cases or for information to expand
current cases.

Under current regulations, manu-
facturers can use a disclaimer when they
submit a safety report to deny that the
report constitutes an admission that the
product at issue caused or contributed
although the agency has requested
comments from industry on this issue.
If the scope of the safety reporting sys-
tem is to be expanded as proposed, the
regulations need to include a strongly-
worded and unambiguous disclaimer
regarding the proper and improper uses
of SADR reports. Given the expanded
definition of an SADR, it would be
improper and misleading to consider
such reports as legitimate evidence
of causation. These reports often are
spontaneous, uncontrolled accounts of
a particular event in a particular person,
and do not properly constitute evidence
that the drug caused the adverse event.
To guard against potential misuse of
SADR information in product liability

[I]t is unclear whether FDA will be able to manage and make
effective use of the information generated by the expanded
safety reporting requirements.

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cases, a stronger regulatory disclaimer could be displayed prominently on all forms and documents containing case data or safety findings.

Apart from the disclaimer, the proposed rule has several additional implications with respect to product liability lawsuits. First, the proposed rule would consider SADR information compiled in support of class action lawsuits to be neither spontaneous nor "study" information—such that only summary information would need to be provided for these SADRs in periodic reports—because it believes SADR reports from class action suits likely would be duplicative and difficult to investigate. The agency, however, has not applied this logic and approach to SADRs that present comparable difficulties, such as SADRs compiled in support of nonclass action litigation or reported in Internet chat rooms.

Second, the proposed rule does not include an affirmative statement supporting an exemption from discovery for supporting medical information and records collected as part of the SADR reporting process. Without such an exemption, medical providers likely will be hesitant to provide the necessary information, or even to report SADRs at all, in light of medical malpractice concerns.

Third, the proposed rule lacks clear statements that 1) FDA recognizes that adverse event reports should not come into evidence in any type of civil litigation (because such uses are at cross-purposes with FDA's regulatory goals), or 2) SADR reports should not be admissible through the use of "back door" approaches (e.g., expert testimony, expert use of SADR reports to establish causation, hearsay exceptions, etc.).

Finally, the proposed rule fails to acknowledge that drug manufacturers should be able to refer to SADRs in product liability lawsuits to:

- explain the adequacy of precautionary labeling;
- establish that they duly recorded and forwarded adverse events to FDA (where a decision was made that a labeling change was not warranted); and
- establish the absence of any related SADR reports despite diligent postmarketing monitoring.

While matters of discovery and evidence in product liability litigation are not within FDA's authority, clear statements by the agency on the proper and improper uses of information derived from its safety reporting system likely would be considered persuasive by a court in considering the admissibility of such information.

Absent changes to address these vulnerabilities imposed by the proposed rule, drug manufacturers could see an increase in product liability lawsuits and could face additional challenges as defendants in these cases.

HIPAA and Non-U.S. Privacy Laws

In addition to individual case information, the proposed rule would require submission of medical record documents that likely will contain individually identifiable health information. Considerable uncertainty remains about limiting the disclosure of protected health information (PHI) by healthcare providers under the Health Insurance Portability and Accountability Act (HIPAA) and non-U.S. privacy laws (e.g., European Union, Canada, Japan, etc.). This uncertainty could make it difficult for drug manufacturers to obtain the required supporting documentation (e.g., autopsy reports, death certificates, hospital discharge summaries, etc.) for safety report submissions.

For example, it is unclear whether the HIPAA exemption for disclosure of PHI for compliance with other laws (e.g., FDA safety reporting rules) would be applicable where a healthcare provider furnishes PHI to a drug sponsor/manufacturer for submission to FDA. FDA's safety reporting regulations apply to drug sponsors and manufacturers, and not to physicians and other healthcare professionals who would possess much of the information required for SADR reports.

Enforcement Implications

Several new recordkeeping and procedural requirements in the proposed rule, as well as FDA's plan to hire additional enforcement staff, suggest that safety reporting would become a new inspection and enforcement priority for the agency.

Under the proposed rule, manufacturers would be required to maintain documents referenced in expedited report narrative listings and, upon request, provide such documents to FDA within five calendar days. Moreover, written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing adverse drug experiences would need to be maintained for FDA review.

The proposed rule also would require that manufacturers of prescription drugs marketed without an approved new drug application (NDA) or abbreviated new drug application (ANDA), provide FDA with a list of current addresses where safety reports/records are maintained. This would provide rapid access to safety-related records for FDA inspections and for other FDA requests for safety information.
Product Lifecycle Effects

Drug manufacturers have a keen interest in ensuring that their products can be used safely and effectively and do not have unintended consequences. One outcome of the new safety reporting requirements could be the earlier detection of safety issues.

Upon marketing approval, clinical data is available only for limited numbers of patients for relatively short periods of time, and certain high-risk patients and selected concomitant medications may not have been studied. Consequently, the detection of less common adverse events generally is not possible prior to approval. After the start of commercial marketing, new safety information becomes available through worldwide use. In the last decade, adverse event reporting trends indicate an increasing number of reports and an increasing number of 15-day expedited reports.

The proposed expansion in the scope and depth of safety reporting could have profound effects, both pre- and postapproval. In the pre-approval context, the expanded reporting requirements could raise more questions and testing requirements in the investigational new drug (IND) phase. Postapproval, the new requirements could shorten the time to the detection of safety concerns, including increases in labeled events (e.g., severity, outcomes, etc.), serious unlabeled events (e.g., for special populations, long-term exposure, etc.).

This additional safety information could result in accelerated postapproval risk assessments and labeling revisions. Consequently, this safety information could affect projected marketing campaigns and product line extensions.

Conclusion

While FDA's proposed safety reporting rule is premised on worthwhile goals, several of the agency's specific proposals seem misplaced. Regardless of future refinements, the implementation of equivalent requirements would have significant product liability, privacy, enforcement, and product lifecycle implications for the drug industry. △

2 Id. at 34,005.
3 Id. at 34,008.
4 Id. at 34,016.
6 Nor. c.f. 21 C.F.R. § 310.300(g)(1) (2005).
Exhibit 8
FDA’s Final Rule Implementing The Prescription Drug Marketing Act

Publication Date: December 20, 1999

I. INTRODUCTION

On December 3, 1999, the Food and Drug Administration ("FDA") published its final rule implementing the Prescription Drug Marketing Act, Pub. L. 100-293, ("PDMA").(fn1) Congress passed the PDMA to prevent the diversion of prescription drugs for use other than under the supervision of a prescribing physician. The PDMA imposes restrictions on a wide range of activities related to the distribution of drugs and drug samples. The regulations will be of significance to many different segments of the health care community, including drug manufacturers and distributors, hospital pharmacies, the pharmacies of other health care entities such as long-term care facilities, physicians and charitable institutions that provide prescription drug products to indigents.

The PDMA rulemaking process began with a set of proposed rules that FDA published in 1994. The final regulations retain many provisions from the proposal while modifying others significantly. The final rule includes the following important provisions:

- Requirements for distribution of drug samples to physicians and pharmacies of hospital and other health care entities, including conditions for physician request and receipt forms;
- Requirements for manufacturers and distributors to review their inventory of drug samples, investigate discrepancies, significant losses and thefts, and file reports with FDA;
- Conditions on donations of prescription drugs to charitable institutions;
- Bans on the sale, purchase or trade of drug samples or drug coupons (with certain exceptions);
- Standards for distribution of prescription drugs by authorized distributors of record, as well as by unauthorized distributors;
- Restrictions on the reimportation of prescription drugs to the manufacturer or for emergency care; and
- Criminal and civil penalties for violations.(fn2)

This memorandum provides a general overview of the provisions of the new rule.

II. EFFECTIVE DATE OF THE RULE

The final rule is complex. It will create a need for significant changes and organizational revisions by many manufacturers and distributors. Accordingly, FDA has set a one year period for it to take effect. The effective date of the rule is December 4, 2000.

III. DISTRIBUTION OF SAMPLES
A drug sample is defined as a unit of a "prescription drug that is not intended to be sold and is intended to promote the sale of the drug." (fn3) Under the PDMA, manufacturers and distributors may distribute drug samples to practitioners licensed by law to prescribe them, or to hospital pharmacies or health care entity pharmacies at the request of a physician. Retail pharmacies, however, may not receive samples. Samples may not be distributed in response to open-ended or standing requests. Instead, the manufacturer or distributor must receive individual written requests from the practitioner for each sample or group of samples. (fn4)

A. Labeling Of Samples

Each unit of a drug sample must be marked to indicate that it is a sample, e.g., "sample," "not for sale," or "professional courtesy package." (fn5) In response to comments, FDA stated that it would not object to the use of stickers with the word "sample" or equivalent language on container labels. These labels should be difficult to remove, and attached so that removal would be evident if it occurred. The goal is to deny would-be diverters a market-ready product. (fn6)

The regulations require manufacturers and distributors to include on the label of the sample unit and its outside container or packaging (if any), an identifying lot number or control number for tracking the distribution of each unit. (fn7) The proposed rule would have required the use of lot and control numbers on all labeling, including package inserts. In response to comments, FDA dropped that provision as too burdensome. It limited the requirement to product containers and outside packaging.

In the preamble, FDA also discussed "starter packs." These are prescription drug products distributed by manufacturers or distributors to pharmacists without charge, to be stocked and sold at retail. Starter packs are not drug samples under the PDMA because they are intended for resale. FDA noted that some companies have used terms such as "starter," "starter samples," and "patient starter pack" to refer to drug samples. FDA advised manufacturers and distributors not to use these terms on sample labels because they are identified with products that are not samples. (fn8) In addition, FDA noted that while starter packs are not subject to the PDMA, because they are not drug samples, they are nonetheless vulnerable to many of the same concerns over diversion. The agency recommended that manufacturers and distributors institute accounting, audit and security systems to guard against diversion.

B. Distribution Of Drug Samples By Mail Or Common Carrier

1. Requests And Receipts

The regulations permit manufacturers and distributors to distribute drug samples through the mail or by common carrier, provided that the following conditions are met:

- The licensed practitioner executes and submits a written request prior to distribution of the drug sample;
- The manufacturer or distributor verifies with the appropriate state authority that the authorized practitioner is actually licensed to prescribe the drug product;
- The recipient of the sample executes a written receipt at the time of delivery; and
- The receipt is returned to the manufacturer or distributor. (fn9)
The burden is on the manufacturer or distributor to verify the practitioner’s authority to prescribe the drug requested. In response to comments, FDA noted that once a practitioner’s number is verified, the manufacturer or distributor may use internal tracking numbers so that it does not have to reverify the authority each time a sample is requested. However, any list of licenses or authorization numbers must be updated at least annually to reflect possible changes in license or Drug Enforcement Administration ("DEA") status.(fn10)

2. Content Of Requests And Receipts

Manufacturers may give practitioners pre-printed forms on which to make requests for drug samples. These forms may be sent by mail, common carrier or electronic means. However, those sent electronically must meet requirements for security and authentication of electronic records.(fn11)

The regulations also set minimum content requirements for the practitioner requests and receipts. A written request for a drug sample must contain:

- The requesting practitioner’s name, address, professional title and signature;
- The practitioner’s state license or authorization number, or, if a scheduled drug product is requested, his or her DEA number;
- The proprietary or established name and strength of the drug sample requested;
- The quantity of drug requested;
- The name of the manufacturer and distributor; and
- The date of the request.(fn12)

These conditions are the same as those listed in the statute, except that FDA has added the requirement to include the practitioner’s license number.

Manufacturers may use bar codes on preprinted request forms to identify the name and strength of the drug requested, provided that the information is also translated into words, so that the practitioner knows what he or she is requesting. The bar coding must be placed so that it will not cover up, or otherwise interfere with, practitioners’ ability to read the words on the form.(fn13)

Receipts acknowledging delivery of a drug sample must contain:

- For samples delivered to practitioners: (1) the name, address, professional title and signature of the practitioner or practitioner’s designee who acknowledges receipt; (2) the proprietary or established name and strength of the drug sample delivered; and (3) the date of delivery; or

- For samples delivered to pharmacies of hospitals or other health care entities: (1) the name and address of the requesting practitioner; (2) the name and address of the hospital or health care entity designated to receive the drug sample; (3) the name, address, professional title and signature of the person acknowledging delivery of the drug sample; (4) the proprietary or established name and strength of the drug sample delivered; and (5) the date of delivery. (fn14)

Manufacturers and distributors must retain the receipts and requests for three years. They must be available on request to federal and state officials engaged in the regulation of drugs or the enforcement of laws governing drugs.
One commenter asked whether a manufacturer must stop sending drug samples to a practitioner who fails to return a receipt. FDA stated that this is not necessary for isolated incidents. The clear intent of the PDMA is to identify patterns of conduct that may signify diversions. The purpose of the receipt process is to prevent diversion, loss or theft. Its goal is not absolute compliance with procedure, but rather to safeguard those underlying concerns. A single failure to return a receipt need not trigger action. However, a manufacturer who detects a pattern of non-returns should halt distributions of samples to the practitioner and investigate. (fn15)

In response to comments, FDA stated that manufacturers or distributors may utilize a common carrier's electronic delivery verification systems to fulfill the written receipt requirement. However, the system must be able to transmit all of the information required by the regulation. According to the comments, the electronic delivery verification systems available at this time are not configured for all of the mandatory information. (fn16) FDA does permit the combination of electronic and paper media to create a receipt form. These combinations must: (1) meet the requirements of 21 C.F.R. § 11 for electronic recordkeeping; and (2) provide a reasonably secure link between the paper and electronic records such that the combination is trustworthy and reliable and the signer cannot readily repudiate the signed record as not genuine. (fn17) Thus, to the extent that it is practical, a manufacturer or distributor could utilize an electronic delivery verification system, and supplement it with a written receipt for any information that would be lacking.

3. Inventory And Reconciliation

The regulations require manufacturers and distributors to establish, maintain and adhere to written policies and procedures describing their administrative systems for distributing drug samples by mail or common carrier, including a methodology for reconciling requests and receipts. (fn18) The rule does not set specific criteria for these policies and procedures.

C. Distribution Of Drug Samples By Representative Or Dealer

1. Single Form For Requests And Receipts

Manufacturers and distributors may also distribute drug samples through their representatives or dealers. To do so, they must obtain written requests and receipts with the same information as those for samples distributed through the mail or by common carrier. (fn19)

In distributing samples, a representative may use a single form for both the request and the receipt. Moreover, if the request and delivery to a practitioner are simultaneous, the form can be executed with a single signature for both. However, the request form may only be signed by a licensed practitioner. If the request and receipt are combined, that is the only signature that is acceptable. Deliveries to the pharmacy of a hospital or health care entity cannot be simultaneous with the request by the licensed practitioner, so a single signature is not permitted. (fn20)

2. Inventory And Reconciliation Of Drug Samples

Manufacturers and distributors who distribute drug samples through representatives must conduct a physical inventory of all drug samples, at least annually. All samples in the possession or control of representatives must be inventoried and recorded by proprietary or established name, dosage strength

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and number of units. (fn21)

In addition to the inventory, manufacturers and distributors must reconcile the results of the physical inventory with the most recently completed prior physical inventory. They must create a reconciliation report which will include:

- The inventory record for the most recently completed prior inventory;
- A record of each drug sample shipment received since the most recently completed prior inventory, including the sender and date of shipment, and the proprietary or established name, dosage strength and number of sample units received;
- A record of drug sample distributions since the most recently completed inventory showing the name and address of each recipient of each sample unit shipped, along with the date of shipment and proprietary and established name, dosage strength and number of sample units shipped; and
- A record of drug sample thefts or significant losses reported by the representative since the most recently completed prior inventory, including the approximate date of the occurrence and the proprietary and established name, dosage strength and number of sample units stolen or lost. (fn22)

Manufacturers and distributors must also prepare a summary record to help check the accuracy of the reconciliation. It summarizes the information described above, including, for each type of sample unit (i.e., sample units with the same proprietary and established name and dosage strength), the total number of sample units received, distributed, lost or stolen since the most recently completed prior inventory.

The reconciliation report may consist of several different documents, provided that they contain all of the required information when taken together, and they are maintained in a single report. Manufacturers and distributors may use bar coding to represent the proprietary and established name and dosage strength of a drug product in the inventory and reconciliation reports. However, the bar codes must be capable of: (1) detecting discrepancies; (2) translation into words; and (3) being produced in their entirety to FDA on inspection. (fn23)

A significant change from the proposed rule is that FDA does not require inventory and reconciliation to be conducted by persons other than the manufacturer or distributor’s "representatives, their superiors or managers, or others in their direct line of supervision or command." This would have created a significant burden, essentially requiring companies to bring in outsiders not involved in distribution of samples to conduct inventory and reconciliation. The final rule permits representatives and supervisory personnel to conduct inventory and reconciliation, provided that there are appropriate internal controls. (fn24)

FDA did not set specific requirements for internal controls for inventory and reconciliation. The preamble states that they should include a security and audit system controlled by independent personnel, i.e., personnel other than the representatives, their superiors or managers, or others in their direct line of supervision or command. The regulations require manufacturers and distributors to establish, maintain and adhere to written policies and procedures describing their administrative systems for:

- Reconciling requests and receipts, identifying patterns of nonresponse, and establishing the manufacturer or distributor's response when such patterns are found;
- Conducting the annual physical inventory and preparing the reconciliation report;
- Implementing a sample distribution security and audit system, including random and for-
cause audits of sales representatives by personnel independent of the sales force; and
- Storage of drug samples by representatives.(fn25)

FDA leaves the details of these systems to the individual companies. While outside personnel need not conduct reconciliations, the audit system maintains the requirement for external review.

D. Investigation And Notification

1. Investigation Of Falsified Records Or Diversion

A manufacturer or distributor with "reason to believe that any person has falsified drug sample requests, receipts, or records, or is diverting drug samples," must notify FDA, by phone or in writing, within 5 working days, immediately initiate an investigation, and provide FDA with a complete written report including the reason for and result of the investigation, not later than 30 days after the investigation began.(fn26)

FDA did not define what level of suspicion of falsehood or diversion is sufficient to trigger an investigation. Companies have flexibility to evaluate each situation. The agency reiterated that investigations are necessary where a pattern of discrepancies exist or where other reliable information indicates possible falsehoods. (fn27)

It is important to note that the investigation requirement applies to any misconduct a manufacturer or distributor may discover, and not only to that of its employees. In response to comments, FDA stated that because manufacturers are in the best position to identify diversions or falsehoods by its employees or others, the burden falls primarily on them. They must investigate whenever they have reason to believe that any person has falsified records or diverted product. Thus, for example, a manufacturer that had reason to believe a physician to whom it distributed samples was engaging in diversion would have a responsibility to investigate. (fn28)

2. Investigation Of Significant Loss Or Known Theft

The regulations require manufacturers and distributors that distribute drug samples and become aware of a "significant loss or known theft," to notify FDA, by phone or in writing, within 5 working days, immediately initiate an investigation, and provide FDA with a complete written report including the reason for, and result of, the investigation, not later than 30 days after the investigation began.(fn29)

This requirement for investigation applies to actual thefts or losses, not suspected ones. Thus, there is a higher level of certainty to trigger notification, i.e., actual awareness rather than "reason to believe." Thus, by the time a manufacturer notifies FDA and begins an investigation under this provision, it is assumed that a theft or significant loss has taken place. Insignificant discrepancies or bookkeeping errors should have been weeded out prior to taking action.
FDA declined to set a threshold for when an inventory loss is "significant" for purposes of the regulation. Losses may occur in a number of ways, including losses of shipment in transit, loss by representatives and unexplained inventory discrepancies. For shipping losses, companies may wish to set a policy that losses above a certain dollar amount will be deemed significant. This amount would vary by company, depending upon its size, the number of representatives that it has, and the size and value of its total inventory. However, shipping losses should also be considered over a "fixed, rolling period of time," to determine whether a pattern of losses might indicate diversion. Diversion may be indicated in several ways, including: (1) a single loss that exceeds the company's threshold; (2) a number of loss events over a fixed, rolling period of time that exceeds the company's threshold; or (3) a volume of lost products over a fixed, rolling period that exceeds the company's thresholds. (fn30)

However, FDA noted that thresholds should not be applied mechanically. Manufacturers and distributors should consider the nature of lost materials. For a drug with a high potential for diversion, loss of a moderate amount of sample may be far more significant than the loss of greater quantities of another sample with a low potential for diversion. A qualitative evaluation must be applied along with the use of quantitative thresholds.

Regarding unexplained inventory shortages, FDA expects firms to set thresholds for distinguishing between insignificant accounting mistakes and significant losses. These determinations may be based on a firm's experience in sample distribution and the accuracy of its internal audit and security system. Moreover, some firms might be able to set a "historically validated statistical baseline" for minimal amounts of inventory shrinkage attributable to routine accounting errors, mistakes or losses, and a statistical baseline for frequency of occurrences. This could be used as a tool to determine when losses are significant and merit investigation. (fn31)

In response to comments, FDA stated that it will not pledge not to challenge a manufacturer for following its own thresholds, but noted that the best way to ensure that no enforcement action will be taken is to establish and follow a system consistent with the rules and discussions in the preambles. (fn32)

IV. DISTRIBUTION OF DRUG SAMPLES TO CHARITABLE INSTITUTIONS

Charitable institutions may receive drug samples for dispensing to their patients, either as donations from licensed practitioners or from other charitable institutions. Donated drug samples must meet the following conditions:

- The donated sample must be received by the charitable institution in its original, unopened packaging with its labeling intact;
- The donated sample must be delivered by mail or common carrier, collection by the recipient charitable institution or personal delivery by a licensed practitioner or agent of a donating charitable institution;
- The donor must place the drug sample in a sealed carton for delivery or collection;
- A donated sample may not be dispensed to a patient until it has been examined by a licensed practitioner or registered pharmacist at the recipient charitable institution to confirm that: (1) the donation record accurately describes the sample delivered; and (2) the drug sample is not adulterated or misbranded for any reason, including:
- Being out of date;
- Labeling that has become mutilated, obscured or detached;
- Evidence of having been stored or shipped under conditions that might adversely affect stability, integrity or effectiveness;
- The sample is of a drug product that has been recalled or is no longer marketed; or

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The sample is otherwise possibly contaminated, deteriorated or adulterated. (fn33)

If a sample is found to be unsuitable, the recipient charitable institution must destroy it or return it to the manufacturer. The regulations require charitable institutions to keep records of the disposition of all destroyed or returned samples. (fn34)

When a drug sample is delivered or collected, the recipient charitable institution must prepare a complete and accurate donation record containing: (1) the name, address and telephone number of the donating licensed practitioner or charitable institution; (2) the manufacturer, brand name, quantity and lot or control number of the drug sample donated; and (3) the date of donation. The charitable institution must retain a copy of the receipt for at least three years. (fn35)

The regulations require charitable institutions to maintain complete and accurate records of donation, receipt, inspection, inventory, dispensing, redistribution, destruction and returns sufficient for complete accountability and auditing of its drug sample stocks. In addition, all recipient charitable institutions must conduct, at least annually, an inventory of drug sample stock and prepare a reconciliation report comparing it to the results of the most recent prior inventory. Discrepancies and reconciliation problems must be investigated and reported to FDA. If the charitable institution becomes aware of a "significant loss" or "known theft" of drug samples, it must notify FDA within 5 working days. (fn36) The regulations do not set a threshold for determining what is a significant loss and there is no discussion in the preamble. However, FDA addressed the issue in some detail regarding investigations by manufacturers, as described above.

Finally, it is worth noting that the procedures described above are not the only ways charitable institutions may receive donated drug samples. In the preamble to the proposed rule, FDA stated that charitable institutions may receive: (1) direct donations of prescription drugs from manufacturers and distributors, with records of distribution and receipt maintained in accordance with state regulations; and (2) deliveries of drug samples to charity hospital and health care entity pharmacies from manufacturers or distributors, at the written request of a licensed practitioner, in accordance with the regulations on distribution of drug samples. (fn37)

V. RESTRICTIONS ON SALES OF PURCHASED OR DONATED DRUGS

The statute and regulations generally provide that no person may sell, purchase, trade or offer to sell, purchase or trade any prescription drug that was purchased by a public or private hospital or other health care entity, or donated or supplied at a reduced price to a charitable organization. (fn38)

There are a number of exceptions to this general rule. The prohibition does not apply to:

- Purchase or other acquisition of drugs between hospitals or health care entities that are members of the same group purchasing organization ("GPO"), or a purchase or acquisition from the GPO itself;
- Sale, purchase or trade, or an offer to sell, purchase or trade a drug: (1) by a charitable organization to a nonprofit affiliate of the organization as permitted by law; (2) among hospitals or other health care entities that are under common control; (3) for emergency medical reasons; or (4) the dispensing of a drug under a valid prescription; (5) by hospitals or health care entities owned or operated by federal, state or local governmental units to other hospitals or health care entities owned or operated by federal, state or local government units; and
Sale, purchase or trade of, or the offer to sell, purchase or trade blood or blood components intended for transfusion.(fn39)

The return of a prescription drug that a hospital or health care entity purchases at a reduced price, or that is donated to a charitable institution could be viewed as a sale, depending upon whether and how credit is given for the return. However, the general rule prohibiting sales of donated or purchased drugs does not apply to returns by hospitals, other health care entities or charitable institutions of prescription drugs, provided that the following requirements are met:

- The hospital, health care entity or charitable institution documents the return by a credit memo specifying: (1) the name and address of the hospital, health care entity or charitable institution; (2) the name and address of the manufacturer or wholesale distributor from which the drug was acquired; (3) the product name and lot or control number; (4) the quantity of drug returned; and (5) the return date;

- The hospital, health care entity or charitable institution forwards a copy of each credit memo to the manufacturer and retains a copy for its own records (the FDA noted that the credit memo should be forwarded to the manufacturer to help ensure that any chargebacks or reduced prices are factored into a credit or refund provided by the manufacturer to prevent windfall profits from the transaction);(fn40) and

- Any drugs returned to a manufacturer or wholesale distributor must be kept under proper conditions for storage, handling and shipping, and written documentation showing adherence to such conditions is provided to the manufacturer or wholesale distributor.(fn41)

VI. WHOLESALE DISTRIBUTION OF DRUGS

A. Authorized Distributors Of Record And Unauthorized Distributors

The new regulations set conditions for the wholesale distribution of prescription drugs. They are intended to help trace the distribution chain of prescription drugs and increase the accountability of unauthorized wholesale distributors.

The PDMA divides wholesale distributors into two groups: authorized distributors of record, and unauthorized distributors. An authorized distributor of record is defined as one with whom a manufacturer has established an ongoing relationship to distribute its products. (fn42) An ongoing relationship must be evidenced

Related Information

Related Contacts

- Metro, Joseph W.
- Bloch, David J.

Related Practice Area(s)

- Health Care

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Exhibit 9
The Food and Drug Practice of
Sidley Austin Brown & Wood LLP

Sidley Austin Brown & Wood LLP has a comprehensive practice of food and drug regulation. From our offices in Washington, D.C., New York and Brussels we counsel multinational corporations and trade associations on all aspects of U.S. and EU food and drug law. We can assist clients in dealing with questions of interpretation of the new EU Regulations and can interface with EU government officials regarding the development of implementing rules. Finally, we can assist clients to develop internal procedures to ensure compliance with these new EU Regulations.

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FDA Interim Final Rule on BSE and Use of Materials Derived from Cattle in Human Foods and Cosmetics


The Interim Final Rule—which goes into effect immediately—bans the use of certain cattle parts from FDA-regulated food, dietary supplements and cosmetics. Use of prohibited materials in these FDA-regulated products cause them to be considered adulterated and subject to enforcement action.

The FDA’s rule follows the publication of a similar rule by the Food Safety and Inspection Service (FSIS) of the United States Department of Agriculture (USDA) on January 12, 2004. That rule prohibited certain components of cattle from the U.S. food supply. In its Interim Final Rule, the FDA extends similar prohibitions to FDA-regulated human foods and cosmetics.

Prohibited Materials

Prohibited materials under the FDA’s rule include:

- Suspected Risk Materials (SRMs): brain, skull, eyes, trigeminal ganglia, spinal cord, vertebral column and dorsal root ganglia of cattle 30 months and older, and the tonsils and distal ileum of the small intestine of all cattle;
- Small intestine of all cattle;
- Mechanically Separated Beef (MS Beef);
- Beef from non-ambulatory disabled cattle; and
- Beef from cattle not inspected and passed.

The FDA is exempting tallow (used generally for soaps and fatty acids) that is free from prohibited material or that contains not more than 0.15% hexane-insoluble impurities.

Effective Date

The rule goes into effect immediately, though the FDA will accept comments until October 12, 2004.
Applicability

The rule applies to conventional foods, dietary supplements and cosmetics. As such, gelatin capsules used for foods and dietary supplements must not be made from any of the prohibited materials.

At this time, the Interim Final Rule does not apply to drugs. There is an existing guidance, which was published in 1997, recommending sourcing and processing of gelatin in drugs to minimize the risk of BSE.

This guidance, which is currently under review, allows for the possibility of using bones and hides from non-neurologically impaired cattle from any country as long as the slaughterhouse removes the heads, spines and spinal cords directly after slaughter, and if processors ensure there is no contamination of the gelatin produced with brain, spinal cord or ocular tissue. Further, the guidance does not object to the use of gelatin produced from bovine hides and bones if the gelatin is produced from U.S.-derived raw materials or from cattle born, raised and slaughtered in other countries that have no reported BSE cases and meet BSE-related international guidelines.

The FDA is applying the prohibitions introduced in the Interim Final Rule to all food and cosmetic products or ingredients of food and cosmetic products manufactured in the U.S. or imported into the U.S.

In an advance notice of proposed rulemaking (ANPR) also published on July 14, 2004, the FDA asks for comments on whether there should be an exemption from the Interim Final Rule for products or ingredients of products manufactured in "BSE-free" countries. Comments to FDA specifically on this subject are due by August 13, 2004.

Recordkeeping Requirement

The Interim Final Rule requires that manufacturers and processors of human foods and cosmetics that contain or are processed with cattle material to maintain records documenting that no prohibited materials are used.

Because the FDA recognizes that recordkeeping procedures cannot be put into effect immediately, the agency is also proposing the recordkeeping requirements in a separately-published proposed rule. Comments on recordkeeping and records maintenance requirements in the proposed rule are due on August 13, 2004.

The FDA states that it has left the recordkeeping requirement in the Interim Final Rule so that it can gain access to records that may already exist.

Effects of Non-Compliance

The Interim Final Rule declares that use of prohibited materials from cattle cause a conventional food to be adulterated under 21 U.S.C. § 342(a)(4). The FDA declares that foods containing the prohibited materials are additionally not "generally recognized as safe" (GRAS) or approved as food additives, and therefore render the food adulterated under 21 U.S.C. § 342(a)(2)(C).

The FDA declares that dietary supplements are adulterated under 21 U.S.C. §§ 342(a)(3) and (4) if they contain any of the prohibited materials.

Finally, cosmetics are adulterated under 21 U.S.C. § 361(c) if they contain prohibited cattle materials.

Non-compliance with the rule subjects a company to enforcement action by the FDA.
Exhibit 10
Horn v. Thoratec: FDA's Bold New Position on the Pre-emptive Effect of Product Approvals

May 2005
By Bert W. Rein, Karyn K. Ablin, and Sarah E. Botha

By and large, the FDA has confined its participation to cases where it had specifically considered — and rejected — the plaintiffs' claims that a product's labeling or advertising should have included different language from that which was used. See Daniel E. Troy, FDA Involvement in Product Liability Lawsuits, Update: Food & Drug. L., Reg. & Educ. (Food & Drug Law Inst., Wash., D.C.), Jan./Feb. 2003, at 1. In 2004, however, the FDA submitted a brief in a state products liability action that signals the agency's willingness to be much more aggressive in protecting its jurisdiction from lay judge and jury determinations concerning a product's risk-benefit balance that conflict with the FDA's own determination of where that balance lies. See Br. of Amicus Curiae U.S. Dept of Justice, Horn v. Thoratec Corp., 376 F.3d 163 (3d Cir. 2004) (No. 02-4597) ("FDA Br.").

Background

The medical device at issue in Horn was a HeartMate heart pump. After extensive review and numerous communications with the manufacturer, the FDA approved the pump in 1994 pursuant to the Pre-Market Approval ("PMA") process set forth in 21 U.S.C. §360e(c). See Horn v. Thoratec Corp., 376 F. 3d 163, 164-65, 169-70 (3d Cir. 2004). The plaintiff brought design defect and failure to warn claims against the device manufacturer following her husband's death a few days after the HeartMate implanted into him became disconnected from his heart. Id. at 165. The district court granted summary judgment in favor of the device manufacturer, finding that such claims were pre-empted by the Medical Device Amendments' ("MDA's") express pre-emption provision set forth in 21 U.S.C. §360k(a). Id. That provision prohibits states from establishing or maintaining any safety or effectiveness requirement for a medical device that is "different from, or in addition to, any requirement applicable" under the FDCA. 21 U.S.C. §360k(a)(1). The plaintiff appealed the ruling to the U.S. Court of Appeals for the Third Circuit. Horn, 376 F.3d at 165.

Before reaching a decision, the Third Circuit requested the FDA's views on whether the plaintiff's claims were pre-empted by the MDA's express pre-emption clause. FDA Br. at 1. The court acknowledged that "FDA's pre-emption determinations are significant and should inform our interpretation of §360k(a)" and cited the Supreme Court's statement that the agency was "uniquely qualified to determine whether a particular form of state law stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress, and, therefore, whether it should be pre-empted." Horn, 376 F.3d at 171 (quoting Medtronic v. Lohr, 518 U.S. 470, 495-96 (1996)).

FDA's Position on Pre-emption

In a 31-page submission, the FDA argued that the state common law claims were pre-empted and that it believed "that this view is compelled in order to achieve Congress' important public health protection purposes, carried out through FDA's implementation of the FDCA." FDA Br. at 1-2. The FDA asserted that the Supreme Court's decision in Medtronic, Inc. v. Lohr, which found that the MDA's express pre-emption provision did not pre-empt state tort law claims brought against medical devices cleared pursuant to Section 510(k) of the FDCA, provided the analytical starting point but did not control the outcome of cases involving PMA-approved devices. Id. at 14-19 (discussing Medtronic, Inc. v. Lohr, 518 U.S. 470 (1996)).

Distinguishing the PMA approval process from the Section 510(k) clearance procedure, whereby devices may be cleared for marketing if they are found to be "substantially equivalent" to a predicate device, the FDA observed that "[p]reparation of a PMA and FDA's process of reviewing a PMA constitute a massive undertaking. ... [the review] is thorough and scientifically rigorous, generally taking an average of 1200 hours of review time by the agency." Br. at 8. The agency further observed that any revisions made after the FDA approves a PMA for a medical device, are considered with "the same type of rigorous scientific process utilized for review of original PMAs." Id. at 10. The FDA then stated that the Section 510(k) procedure, "which typically requires an average of only twenty hours to complete" and "which only determines whether two products are substantially equivalent," was "entirely different from a PMA" approval. ... " Id. at 12, 20.
The FDA argued that, unlike the Section 510(k) substantial equivalence requirements at issue in Lohr, the PMA process did impose sufficiently specific requirements as to pre-empt contrary or supplemental state law requirements imposed via state tort actions. *Id.* at 14-17.

Although the FDA focused its analysis on the MDA's express pre-emption provision, it strongly suggested that the plaintiff's claims were also precluded on conflict pre-emption grounds. That type of pre-emption exists either "when compliance with both state and federal law is impossible, or when the state law stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress." *Capital Cities Cable, Inc. v. Crisp*, 467 U.S. 691, 699 (1984). The agency made an extensive argument indicating its belief that recognition of state design defect and failure to warn claims would, indeed, "stand[] as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress" (*id.*) by thwarting "Congress's important public health protection purposes." FDA Br. at 2, 25-26.

Notably, the agency acknowledged that its view represented a change from its previous position that the PMA process only represented the "FDA's endorsement of a minimum standard" and that therefore "PMA approval should not displace state common law that may provide additional protection to consumers." *See id.* at 29. The FDA explained that its prior opinion did not appropriately consider either "the highly detailed and prescriptive nature of the PMA approval process" or the state-of-the-art risk management principles currently employed by FDA, which properly recognize that minimizing risk through additional warnings or market withdrawal may actually discourage or prevent appropriate product use. *Id.* at 28-29. In light of the FDA's comprehensive review and risk-benefit balancing analysis it conducts with respect to each PMA-approved device, the FDA concluded that it now believes that "a PMA approval sets a ceiling as well as a floor." *Id.* at 29.

**Third Circuit's Decision**

The Third Circuit agreed with the FDA and the lower court that the MDA's express pre-emption provision pre-empted plaintiffs' claims. *Horn*, 376 F.3d at 180. In reaching this conclusion, the court followed in the FDA's footsteps both by distinguishing the case from *Lohr* and by finding that the Section 510(k) process at issue in *Lohr* was not at all comparable to the "far more thorough and rigorous PMA approval process" that the HeartMate had undergone. *Id.* at 167, 169-70, 174-76.

The court also appeared to adopt the FDA's view that the plaintiff's claims would be precluded by principles of conflict pre-emption. While the court did not decide this question, it nonetheless stated that any finding in the plaintiff's favor "would stand as an obstacle to the accomplishment and execution of the objective of the safety and effectiveness of the medical device" specifically and would conflict with the federal requirements imposed by the PMA "— an almost verbatim recitation of the purposes and objectives form of conflict pre-emption. *Id.* at 166, 179 (quoting *Geier v. American Honda Motor Co.*, 529 U.S. 861, 873 (2000)).

**Implications**

The FDA's brief in *Horn* appears to represent a significant shift from the agency's previous reticence in taking aggressive positions on pre-emption. In the recent past, the agency generally had focused on cases where a plaintiff sought to impose a requirement on a product that would have been in direct conflict with a specific prior decision by the agency and that often would have rendered it impossible for the product's manufacturer to comply with both federal standards and a state court judgment in the plaintiff's favor. For example, in *Motus v. Pfizer Inc.*, the agency had examined and "repeatedly found that there was no causal relation between taking the drug at issue and an increased risk of suicide." *See Br. of Amicus Curiae U.S. Dept of Justice* at 2-3, *Motus v. Pfizer Inc.*, 358 F.3d 659 (9th Cir. 2004) (No. 02-55372). It thus argued that the drug would be misbranded under the FDCA if its labeling included the plaintiff's proposed warning suggesting such a relationship. *Id.* at 17-22. In a similar case, the FDA had specifically considered and refused to adopt the plaintiff's proposed warnings on a nicotine replacement therapy product and therefore argued that a ruling in the plaintiff's favor would make it impossible for the defendants to comply with both federal and state law. *Br. of Amicus Curiae U.S. Dept of Justice* at 12-16-19, *Dowhal v. Smithkline Beecham Consumer Healthcare*, 32 Cal. 4th 910 (Cal. 2004) (No. S109306). Furthermore, in litigation over Paxil, the FDA had, on five separate occasions, reviewed challenged advertisements stating that Paxil was not habit forming and refused to find them misleading. *Br. of Amicus Curiae United States of Am.* at 4, *In re Paxil Litig.*, No. CV 01-07937 (C.D. Cal. Aug. 16, 2002). The FDA thus argued that the plaintiff's request that advertisements containing this statement be halted "directly impinges on FDA's role as the protector of the public interest in this field by ordering specific changes to ads that FDA has deemed acceptable." *Id.* at 5.

In contrast to these cases, the FDA in *Horn* espoused a much broader form of conflict pre-emption that does not hinge on the agency's isolated consideration and rejection of the precise argument raised by a state court plaintiff. Instead, the FDA relied on the searching and comprehensive — indeed, prescriptive — nature of the PMA approval process and argued that its risk-benefit balancing determinations concerning a product and its labeling — decisions calculated to protect and promote the overall public health — should constitute the final, authoritative word regarding the product. As the FDA made clear, allowing state lay judges and juries to redetermine a product's risks and benefits or revise a product's FDA-approved labeling based on the experience of a single individual or group of individuals would thwart Congress' goal of protecting the overall public health.
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Significantly, although *Horn* involved a medical device, the agency’s reasoning would appear to apply equally to cases involving prescription drugs approved pursuant to a New Drug Application ("NDA"). Even though the statutory provisions governing prescription drugs do not contain an express pre-emption provision analogous to the provision governing medical devices, the agency’s arguments in favor of pre-emption went beyond express pre-emption to encompass "objects and purposes" conflict pre-emption, as discussed above. Like PMA-approved medical devices, NDA-approved drugs and their proposed labeling undergo searching scrutiny by the FDA in a lengthy back-and-forth process with the manufacturer before they are permitted on the market. Just as the agency does for PMA-approved medical devices, the FDA performs systemic risk-benefit assessments for each NDA drug to determine whether it should be marketed, comprehensively regulates the mix of information accompanying a drug to optimize use and continuously monitors the drug to ensure that ongoing experience does not materially alter the drug’s risk-benefit calculus. Therefore, there is no logical reason why the FDA’s position that "a PMA approval sets a ceiling as well as a floor" (FDA Br. at 29) would not apply equally to NDA approvals, thereby counseling in favor of pre-empting design defect or failure to warn lawsuits brought against NDA-approved drugs.

Only time will tell the extent to which the FDA will continue to invoke broad principles of conflict pre-emption in vigorous defense of its jurisdiction and the extent to which courts will adopt the FDA’s position, as the Third Circuit in *Horn* did. To date, courts have been divided on the extent to which conflict pre-emption precludes common law claims against drug manufacturers whose products are in compliance with FDA regulations. *Compare Ehls v. Shire Richwood, Inc.*, 233 F. Supp. 2d 1189, 1198 (D.N.D. 2002) (finding that failure to warn action was pre-empted and observing that the “FDA dictates the contents of the label for [defendants’ drug product] and defendants were prohibited from changing it without prior approval from the FDA”), aff’d, 367 F.3d 1013 (8th Cir. 2004) with *Merrell Dow Pharms., Inc. v. Oxendine*, 649 A.2d 825, 829 (D.C. 1994) (rejecting pre-emption argument and observing that “the FDA action with respect to [defendant’s drug product] was not intended to resolve the issue of safety for all purposes, and its finding of safety does not irreconcilably conflict with the jury’s finding of liability with respect to Merrell Dow.”). One can only hope that *Horn* is the bellwether case that it appears to be and that courts will accord increasing deference to the FDA’s centralized, expert risk-benefit decisions concerning the safety and efficacy of drugs and medical devices and refuse to allow state judges and juries lacking the FDA’s expertise and experience to second-guess these decisions to the detriment of the overall public health.

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Exhibit 11
REGULATORY

UNITED STATES

FDA Announces New Rules on Exporting Unapproved New Drug Products from the United States

The FDA recently amended its regulations for exporting investigational new drugs, including biologics, from the United States. Such drugs can be exported under four mechanisms:

The first mechanism applies to drugs for which an Investigational New Drug (IND) application is in effect in the United States. In order to be exported, the drug must comply with the laws of the country to which it is being exported and each person who receives the drug must be an investigator in a study under the IND.

The second mechanism applies to investigational drugs that have valid marketing authorization in countries listed by the FDA (Australia, Canada, Israel, Japan, New Zealand, Switzerland, South Africa, or in any country in the EU or the European Economic Area). Again, the drug must comply with the laws of the country to which it is being exported and, among other things, be manufactured according to Good Manufacturing Practices (GMPs) or must meet international standards; and not be sold or offered in US commerce. Prior FDA authorization is not required for such exports.

The third mechanism applies to investigational drugs being exported to one of the above “listed countries” for investigational use. This mechanism requires satisfaction of the same requirements as the second mechanism. Prior FDA authorization also is not required. Importantly, the FDA does not interpret this third mechanism as allowing transshipment (the practice of shipping a product to a listed country from which it will later be shipped to another country).

The fourth mechanism applies to unapproved new drugs exported to any country for investigational use without an IND. The FDA has now eliminated the requirement of prior FDA authorization for these exports. However, the exporter must submit a certificate to the FDA at the time of exportation that affirms various conditions or criteria, including that the clinical investigation will be conducted in accordance with the FDA regulation on foreign clinical studies not conducted under an IND, and that the drugs are “intended for export.” The amended regulations also permit, under the fourth mechanism, the export of investigational drugs to a foreign country in the case of a national emergency (whether for stockpiling in anticipation of, or for use in, a sudden and immediate national emergency).

November 23, 2005, Federal Register

INTELLECTUAL PROPERTY

UNITED STATES

Major US Patent Overhaul Planned for 2006

Last year, a committee of the House of Representatives began drafting legislation that, if enacted, would be the most significant overhaul of US patent laws since 1952. Although the legislation stalled amidst intense lobbying efforts by representatives of industries with disparate interests, the chairmen of both the House and Senate subcommittees with oversight of intellectual property have indicated that they are determined to introduce patent "reform" legislation in 2006. The proposed legislation is intended to respond to concerns over subjective standards in patent examination and patent litigation, and the enormous cost of patent litigation, among other issues.

One of the most significant proposals is conversion of the US patent system from a "first-to-invent" to a "first-inventor-to-file" system. Under the latter system, the first inventor to file an application in either the US Patent
Office or abroad would be entitled to the patent, assuming the application satisfies the other conditions for patentability. The current "patent interference" procedure, which attempts to determine who was the first to "conceive" an invention, would no longer be necessary to determine rights of priority.

Another far-reaching proposal is the creation of a post-grant opposition proceeding, whereby third parties could challenge the validity of issued patents at the Patent Office. The proposed legislation attempts to provide a proceeding for eliminating invalid patents that is both less expensive than litigation and less restrictive than current reexamination proceedings.

Both the first-to-invent and post-grant opposition proposals would bring the US laws closer to European laws, thereby furthering the long-term goal of international "harmonization" of patent laws.

Other proposed changes would reduce the uncertainty and cost associated with patent procurement and litigation. These include revisions of the "prior art" standards, elimination of the "best mode" disclosure requirement, the creation of new procedures for allegations of "inadequate disclosure," and the tightening of the requirements for permanent injunctions and the imposition of increased damages for willful infringement.

For more information on the progress and significance of the proposed patent legislation, visit http://www.wilmerhale.com/patent_act_2005/

EUROPE

New Patent Infringement Exemption Assists Generic Competition

As of October 30, 2005, the infringement provision of the UK 1977 Patents Act has been amended, so that an act committed while "conducting a study, test or trial which is necessary for" and "conducted with a view to" applying for marketing authorization for a generic version of a drug will not infringe a patent covering that drug. This amendment grants generic drug manufacturers a safe harbor, allowing pre-patent-expiration testing in the UK.

For more information on the 2005 Medicines Amendment Regulations, visit http://www.wilmerhale.com/uk_meds_1205

House of Lords Clarifies Law of Novelty

Continuing a spell of unusual activity in patent matters, the House of Lords has recently provided guidance on the issues of "disclosure" and "enablement", clarifying the test for "novelty".

In an action relating to the question of which company — Synthon or Smithkline Beecham — was first to disclose a particular crystalline form of paroxetine mesylate, a key ingredient in a widely prescribed antidepressant, the House has reversed the judgment of the Court of Appeal, upholding that of Jacob J at first instance, thereby invalidating Smithkline's UK patent.

In summary, Synthon had filed an international patent application claiming a broad class of compounds, including paroxetine mesylate; the specification describing how to make this compound in crystalline form. Prior to its publication, Smithkline filed a priority document for a UK patent application, claiming the particular crystalline form. The Court was asked to decide, first, whether the Synthon application disclosed the claimed invention (the "disclosure" issue); and second, whether the ordinary skilled addressee would be able to perform this invention, if he attempted to do so, using the disclosed matter and his common general knowledge (the "enablement" issue). The House held that, on the facts, both requirements had been satisfied.

Importantly, Lord Hoffman further clarified that disclosure and enablement were distinct concepts: each had its own rules and each had to be separately satisfied. In order to satisfy disclosure, the matter relied upon as prior art must disclose subject matter that if performed, would necessarily result in patent infringement. In order to satisfy enablement, this disclosure must then provide sufficient information (in conjunction with common general knowledge), for the ordinary skilled reader to be able to perform the claimed invention.

Synthon v. Smithkline Beecham (2005)

CHINA

New Compulsory Licensing Regulations in China

On November 29, 2005, China's State Intellectual Property Office (SIPO) promulgated new regulations providing for compulsory
sory licensing of patented pharmaceutical products. The Measures on Implementing the Compulsory Licensing of Patents Concerning Public Health Problems, apply the WTO's Doha Declaration on the TRIPs Agreement and public health to China's pharmaceutical industry.

Pharmaceutical products, including their active ingredients and the diagnostic reagents required for their use, related to the prevention and control of the emergence or spread of communicable diseases are made subject to compulsory licensing. Three specific communicable diseases — AIDS, pulmonary tuberculosis and malaria — are listed. However, other communicable diseases resulting in public health problems are also subject to compulsory licensing under the Communicable Diseases Prevention and Control Law.

Procedurally, the competent government authority, presumably the Ministry of Health, would request SIPO to issue a compulsory license to exploit the relevant patent upon a finding of insufficient Chinese production capacity. Royalties would then be set at a reasonable level. A product for which a compulsory license is granted may not, however, be exported, except to a WTO member or less developed non-WTO-member, in accordance with the Doha Declaration.

The Measures entered into effect on January 1, 2006. They constitute the first instance in which China has promulgated product-specific compulsory license regulations, although the government has had the authority for some time to do so.

Although the Measures address a public health contingency and appear WTO-compliant, there is a risk of discouraging innovation in the underinvested pharmaceutical and life sciences industries. Some 69% of invention patents in China in the pharmaceuticals industry (as opposed to Traditional Chinese Medicine) are currently granted to foreigners, not Chinese. On the other hand, the Measures may induce foreign manufacturers of relevant products to invest in production facilities in China so that they can better meet demand in a national public health emergency and be in a better political position to defend their royalty rates.

ANTITRUST/COMPETITION

UNITED STATES

Supreme Court Requests Views of Solicitor General and Second Circuit Court of Appeals Rule on Hatch-Waxman Patent Settlements

In the last issue, we reported that the FTC's constraints on Hatch-Waxman patent settlements between pioneer and generic drug companies had been rejected by the Eleventh Circuit Court of Appeals. The court concluded that any settlement involving generic exclusion that was less than or equal to the scope of the patent was presumptively valid. The FTC thereafter sought review by the US Supreme Court, and its application remains pending. Ironically, the Supreme Court has now asked for the views of the Solicitor General, who normally represents agencies of the federal government before the Supreme Court. The Solicitor General had declined to advance the FTC's position in the initial review petition, after which the FTC elected to pursue review on its own. The request for the views of the Solicitor General may delay for many months the Court's decision on whether to accept the review, pending the Court's receipt of the SG's brief.

Meanwhile, another Court of Appeals — the Second Circuit — has also rejected the FTC position that any settlement including compensation from the pioneer drug patent holder to a generic drug challenger, coupled with "delayed" generic entry, is almost always illegal. In Re: Tamoxifen, a private civil litigation brought by a variety of third party payers and tamoxifen consumers, the Second Circuit affirmed the District Court's dismissal of the claim, endorsing the analysis employed by the Eleventh Circuit in the Schering-Plough case: "[S]imply because a brand-name pharmaceutical company holding a patent paid its generic competitor money [in the settlement of patent litigation] cannot be the sole basis for a violation of the antitrust law unless the exclusionary effects of the agreement exceed the scope of the patent's protection." The plaintiffs have sought rehearing and the FTC has filed an amicus brief in support of that motion.

Schering-Plough Corp. v. FTC
Re: Tamoxifen Citrate Antitrust Litigation
EUROPE

European Commission Receives a Complaint against Pfizer from European Lobby Group

On October 17, 2005, the European Association of Euro-Pharmaceutical Companies (EAEP) filed a complaint with the European Commission, alleging that Pfizer is infringing EU competition law by implementing a deliberate strategy of preventing the export of medicines from Spain to other EU countries.

The EAEP alleges that Pfizer’s actions amount to a dual-pricing system and an export ban, and that Pfizer’s agreements with wholesalers prevent, restrict or distort competition in breach of Article 81 EC Treaty, and that its conduct constitutes an abuse of a dominant position in breach of Article 82 EC Treaty.

The European Commission has not yet commented, but is understood to be considering the complaint.

EAEP Press Release

UK Competition Appeal Tribunal Imposes Directions on Genzyme

On September 29, 2005, the UK Competition Appeal Tribunal (CAT) gave judgment on the remedy to be imposed on Genzyme Limited, following the CAT’s decision of 2004 that Genzyme had infringed UK competition law by pricing Cerezyme (a drug used for the treatment for Gaucher’s disease) and associated homecare services at levels that precluded third party competitors from making a profit.

The CAT’s directions, which are to be monitored by the UK Office of Fair Trading, requires Genzyme inter alia to: (1) set the price of Cerezyme to providers of homecare services at a level that enables third party providers to make a profit on the homecare services; (2) supply Cerezyme to all bona fide providers of homecare services at a drug-only price and at a discount from the prevailing NHS list price; and (3) ensure that sales of Cerezyme to Genzyme’s former homecare business are made on an arm’s length basis.

This is the first occasion on which the CAT has given directions on a remedy to be imposed.

Genzyme Ltd v. OFT

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