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Commentary

FDA Regulatory Action Does Not Establish Causation — FDA Borrows A Page From The Parlodel® Litigation

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It has become an increasingly familiar pattern. After receiving anecdotal reports of adverse events, FDA makes a precautionary decision to add warning language to a drug label or to withdraw the drug's approval. Plaintiffs' attorneys respond with immediate advertisements over the print and broadcast media and the Internet for potential plaintiffs who had similar adverse events while taking the drug. For the product liability plaintiff bar, this is a pre-packaged litigation. The FDA has "determined" causation, so all they need to do is find the plaintiffs and start filing lawsuits. This phenomena was recently addressed by FDA Commissioner Mark McClellen:

> The most experienced and well-financed plaintiffs' law firms know that the biggest payouts can go to those who exploit the FDA's decisions in support of our mission to promote the safe and effective use of medications. More and more often, the "mass tort" firms specialize in taking a new product warning or withdrawal decision, and using it to pile on the company.[1]

The problem, of course, is that the FDA has not determined causation. It has made a precautionary determination that a potential risk, whether or not scientifically proven, is sufficient to warrant regulatory action. These types of regulatory action play an important role in educating the medical community to potential risks and generating hypotheses that can be tested by further study and scientific research. By leaping directly to causation, however, the plaintiff bar has hijacked this regulatory action and diverted FDA's message. Rather than being used to raise questions and spur scientific and medical discovery, FDA regulatory actions are presented as final answers, which, if accepted by courts and juries, can close the book improperly on needed pharmaceutical remedies, and impose unwarranted hurdles to the development and availability of drug treatments.

In this article, I first discuss the FDA's regulatory authority over prescription drug approval and the precautionary principle that governs its efforts to protect the public against potential risks. In the next section, I address FDA's efforts to balance its precautionary principle with the equally significant need to ensure the adequate availability of needed therapeutic drugs and discuss how the agency's ability to pursue these balanced objectives is undermined by the distortion of FDA regulatory determinations in tort litigation. In the final section, I review a series of cases involving the prescription drug Parlodel® in which the courts have recognized the crucial distinction between FDA regulatory action and causation and imposed a legal firewall against improper use of FDA decision-making by plaintiffs' attorneys. Over the past year, FDA has adopted this Parlodel® authority as official agency position in an effort to wrest back control of its regulatory responsibility from the tort lawyers.

I. FDA Regulation Of Prescription Drugs — The Precautionary Principle

FDA regulation of pharmaceutical products for safety and efficacy is based on the precautionary principle that pharmaceutical products should be withheld from the marketplace until and unless sufficient evidence exists to show a margin of safety for use of the drug in the population at large. Accordingly, FDA regulation of prescription drugs is extensive and the consequential costs in bringing a new drug to market in the United States are significant. A recent study by the Tufts Center for the Study of Drug Development calculated that total research and development costs per new drug brought to market in the United States are $802 million.[2] These expenditures provide significant protections against dangerous products reaching the market, but also impose huge financial barriers to the development of necessary pharmaceutical treatments.

FDA regulation of pharmaceuticals begins well before a drug is made available to the medical community. After a potential pharmaceutical has been identified through chemistry, in-vitro experiments and non-clinical animal research, a drug company will file an investigational new drug application with FDA for permission to proceed with clinical testing. If approval is granted, the drug generally must go through three successive phases of clinical studies. In the first phase, the drug is tested on a small number of healthy volunteers to establish proper dose levels and to gain a better understanding of the metabolism and potential toxicity of the drug in humans. If the Phase I studies support further research, the drug then proceeds to Phase II trials, where it is given to a larger group of subjects with the targeted disease for additional safety information and preliminary data on efficacy. If the Phase II studies are successful, the drug may then proceed to Phase III, where it is tested in an even larger group of patients through multi-center trials to establish safety and efficacy pursuant to FDA regulations.

Only after all three phases of clinical testing are successfully completed may a drug company seek approval from FDA to market and sell a prescription drug in the United States. The procedure for seeking drug approval, known as the New Drug Application or NDA process, is significant in and of itself. A pharmaceutical company must submit voluminous documents to the agency in accordance with statutory requirements set forth in the Food, Drug and Cosmetic Act, 21 U.S.C. § 355. New drug applications — which often consist of documents numbered by the truckload — are subject to detailed regulatory requirements addressing, *inter alia*, the format and organization of the application, pharmacologic and toxicologic studies, clinical investigation data, case reports forms, patent information, and marketing-exclusivity issues. *See* 21 C.F.R. § 314.50. FDA will approve a drug only if it determines that the drug is both safe and effective for the indicated use as set forth in the drug label. *See* 21 U.S.C. § 355.

After FDA grants new drug approval, the agency maintains regulatory control over the labeling, marketing, and continued approval of the drug, and the regulatory scheme is designed to detect potential new health risks as soon as possible and convey that information to the medical community through drug labeling and other means. Thus, drug manufacturers remain subject to FDA regulations that require both periodic and expedited submissions of certain adverse drug experience reports, *see* 21 C.F.R. § 314.80, and regular submissions of new studies and numerous other data relevant to the continued approval of the drug, *see* 21 C.F.R. § 314.81. FDA may also require Phase IV post-marketing studies to gather additional information regarding the drug's safety, efficacy, or optimal use. *See* 21 U.S.C. 356b. FDA retains continuing regulatory control over the content and format of drug labels. *See* 21 C.F.R. § 201.57; *see also* 21 C.F.R. Part 201. Further, FDA regulates what manufacturers are permitted to say and do in communicating with physicians about drugs, and it circumscribes manufacturers' advertising and marketing activities. *See* 21 C.F.R. § 200.5 ("Mailing of important information about drugs"); Part 202 ("Prescription Drug Advertising"); Part 203 ("Prescription Drug Marketing").

This post-marketing surveillance and oversight is not limited to scientific evidence that might reliably establish a causal link between a drug and an adverse event. To the contrary, FDA purposefully casts a wide net so that it can obtain and then disseminate preliminary safety infor-

mation that may — or may not — ultimately prove relevant to the actual clinical safety of a drug. Thus, FDA's Med Watch program encourages physicians to report anecdotal cases of patients who suffer adverse events while using a drug whether or not the physician believes that a causal link can be made, and that information is often then placed on the drug label. However, as FDA made clear over a decade ago, the information gathered through the Med Watch program is not scientifically reliable evidence that the drug actually caused the adverse events reported.

In a 1988 publication "Brief Description [of Adverse Reaction Reporting System ("ARRS")] with Caveats of [the] System," FDA explained that "[t]he primary purpose for maintaining the [ARRS] data base is to serve as an early warning or signaling system."[3] These FDA Caveats further state that:

> for any given case report, *there is no certainty that the suspect drug caused the reaction.* This is because physicians are encouraged to report all suspected drug events, not just those that are known to have been caused by the drug. The event reported in a case report may have been related to an underlying disease for which the drug was given, to other drugs being taken concurrently, or may have occurred by chance at the same time the suspected drug was taken."[4]

FDA further explained that "[a]ccumulated case reports cannot be used to calculate incidence or estimates of drug risk. They must be carefully interpreted as reporting rates and not occurrence or incidence rates. Comparisons of drug safety cannot be made from these data."[5] FDA more recently cautioned "because of incomplete data and the uncertainty caused by the underlying illness, indication, or other drug exposures, adverse experience reports may be attributed to a drug or biological product even though it may not necessarily have caused the adverse experience."[6]

On March 14, 2003, FDA proposed a new rule that, among other things, would provide further clarification of the meaning and purpose of adverse drug event reporting.[7] The proposed rule would remove the current definition of "adverse drug event" ("ADE") from its postmarketing safety reporting regulations and replace it with a new definition of "suspected adverse drug reactions" ("SADR"). SADRs would be defined as "a noxious and unintended response to any dose of a drug" where a causal relationship "cannot be ruled out."[8] FDA explained that this new definition would not affect the number of such reports submitted to the agency "because every spontaneous report currently must be submitted to FDA, irrespective of whether the manufacturer or applicant considers it to be drug related."[9]

By casting a wide net for adverse drug event reporting, FDA fulfills its precautionary regulatory function of identifying potential risks promptly, informing trained medical professionals of such potential risks so that they can be factored into individual patient care, and spurring scientific research to provide a scientific foundation for further decision-making. As additional information is received, FDA may also take preventative steps to reduce public exposures to potentially dangerous products. FDA does not wait for scientifically reliable evidence of causation before taking action. Rather, FDA makes conservative risk-benefit assessments. Particularly where there are substitutes on the market or the medical indication is considered less serious, FDA will err on the side of caution and restrict access or even withdraw approval of a drug despite the fact that a causal link between the drug and the health risk has not been established.

II. The Hijacking Of The FDA Regulatory Process

In pursuing its precautionary role of protecting the public against potential health risks, FDA must also be mindful of the adverse consequences of overstating these risks. As the Supreme Court recently explained, FDA's regulation of prescription drugs involves "a somewhat delicate balance of statutory objectives."[10] Congress has charged FDA with the mission of "promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regu-

lated products in a manner which does not unduly impede innovation or product availability."[11] FDA's ability to pursue these different functions, however, has been significantly impaired by plaintiffs' attorneys in prescription drug litigation. Unlike FDA, the plaintiff bar does not have an institutional interest in ensuring the availability of prescription drugs to patients. Nor do plaintiffs' attorneys have an institutional interest in providing a measured understanding of preliminary data regarding potential adverse effects of a drug. Instead, plaintiffs' attorneys have a one-way financial interest in hyping any FDA regulatory action into a government finding that a drug could have caused an adverse effect.

The distortion of FDA regulatory action by plaintiffs' attorneys prevents FDA from achieving its balanced statutory objectives in at least two ways: First, it artificially inflates the meaning of regulatory action, which can result in under-utilization of needed drugs and unduly complicated agency relations with drug manufacturers and special interest groups. Second, it raises the costs to drug manufacturers and thus chills the development of necessary pharmaceutical products.

A. Artificial Inflation Of Regulatory Action

FDA carefully assesses the impact of its regulatory decisions on both the over-utilization and under-utilization of a drug. As FDA has explained, "under-utilization of a drug based on dissemination of scientifically unsubstantiated warnings, so as to deprive patients of beneficial, possibly lifesaving treatment, could well frustrate the purpose of federal regulation as much as over-utilization resulting from a failure to disclose a drug's scientifically demonstrable adverse effects."[12] While FDA has a regulatory interest in promptly disseminating new information regarding potential health risks in drug labels, if that information is distorted through the tort system, FDA must consider the impact of that distorted message on future use of the drug. Even if doctors are able to see through the litigation haze and properly interpret the scientific significance of the new information, their prescribing decisions may be improperly influenced by fear that such information will be interpreted differently by the courts. FDA raised a similar concern in its recently proposed new rule on safety reporting requirements:

> Some members of the public have maintained that submission of voluntary SADR reports by health care professionals or consumers to manufacturers or to FDA might be discouraged because of concern that a person or entity might be implicated in a product liability action. In addition, industry has expressed its concern that these reports, taken out of context and used in a manner for which they were never intended, can create a product liability vulnerability. FDA is concerned that such liability misuse of these reports could imperil the credibility and functionality of this critical public health reporting system.[13]

FDA also must consider the impact that this distortion of its regulatory message will have on its ability to work with regulated entities. If an FDA decision to add warning language is likely to be misinterpreted by courts and juries as a finding that the drug has been shown to cause the adverse effect, drug companies may resist such action. While FDA has the authority to compel drug companies to change warning language or take other regulatory action, it can best accomplish its goals by working in cooperation with drug companies to convey properly received messages to the medical (and legal) community. Also, as FDA has recognized, "what constitutes appropriate labeling for a drug product is not always obvious. Therefore, drug sponsors often have a dialogue with FDA about what should appear on a particular drug label."[14] For this dialogue to succeed, FDA and drug sponsors need to have confidence that the message conveyed by the drug label or by changes in the drug label will be properly understood. To quote FDA Commissioner, Dr. McClellan, "[w]e learn more all the time about drugs, and we want companies to help us in that effort, not to be afraid to work to develop better information on potential safety concerns for fear of triggering lawsuits."[15]

The flip side of this problem is that FDA's ability to respond to arguments for increased warnings by plaintiff-oriented organizations such as Public Citizen is likewise impaired. FDA's ability to work with these organizations necessarily will be colored by FDA's recognition that its regulatory actions may be misinterpreted. FDA may be more reluctant to require labeling changes proposed by plaintiffs' groups because it will not be able to control the way that those changes are "spun" in the courtroom. As a result, the medical community may be deprived of earlier notice of potential adverse events that might otherwise be placed on the label.

B. Chilling Of Drug Development

Despite significant investments in biomedical research in the 1990s, the number of drugs being approved by the FDA has remained largely flat over the past decade and has even declined recently. The top 20 pharmaceutical companies are turning out only 20 new drugs per year between them. Last year, FDA approved only 21 new molecular entities for use as prescription drugs, down from 44 such approvals in 1996. The number of license applications for new biologicals has also declined dramatically, with only 12 filed last year as compared with 27 in 1998.[16]

For this reason, FDA has become increasingly concerned of late about the impact of the distortion of its regulatory determinations in tort litigation on the costs of drug development. In a recent speech to the Physician Insurers Association of America, FDA Commissioner McClellan noted that "[t]he growing practice of pulling together mass lawsuits based on FDA's action is altering the development of medical products in ways that reduce health quality and access."[17]

> Our tort system is having adverse effects on medical care, and it's also impeding affordable and timely access to medical products. This is especially true in important areas like women's health and pediatric care, especially for young children — the same kind of crisis areas as in physician care. As the New York Times reported in a front-page story last weekend, health care experts believe that the unpredictable risk of extreme liability costs is effecting decisions about developing and marketing new treatments. These liability risks particularly affect areas like pregnancy care and vaccines, where we badly need innovation. . . . The legal system is altering the practice of medicine, and the development of medicines themselves, in ways that harm patients.[18]

Dr. McClellan provided the following real world example of how the tort system has hijacked FDA regulatory action:

> One woman, speaking to a reporter for the Jackson Clarion-Ledger, summed it up this way. When she read that the drug Propulsid might cause harm, she stopped taking it and signed up for a lawsuit. "Actually, I didn't get hurt by Propulsid," she told the newspaper. But because she had taken the drug, she said she thought she could join a class-action lawsuit "and I might get a couple of thousand dollars." Today, can we really afford an extra couple of thousand dollars every time a patient uses a drug, even if it doesn't harm them?[19]

Dr. McClellan cautioned that "[t]oday, developers of new medical products increasingly need to set aside billions of dollars, or redirect their research activities from potentially valuable directions, in anticipation of potentially unlimited risk of mass tort litigation."[20]

III. FDA's Reliance On The Parlodel® Litigation To Correct The Distortion Of FDA Regulatory Action

To seize control over the meaning of its regulatory actions back from plaintiffs' counsel, FDA has recently begun relying on a series of prescription drug cases involving the drug Parlodel® in which the courts have properly understood the lack of significance of FDA regulatory action on

questions of causation. In these cases, courts have repeatedly rejected plaintiffs' experts' reliance on FDA warning language and other allegedly adverse regulatory findings and granted summary judgment to the drug manufacturer based on the lack of scientifically reliable evidence of causation under *Daubert v. Merrell Dow Pharms., Inc.*, 509 U.S. 579 (1993).[21]

The Parlodel® litigation involves a prescription drug presently indicated as safe and effective in the treatment of Parkinson's disease, acromegaly, pituitary tumors, amenorrhea and galactorrhea, and infertility. From 1980 to 1994, Parlodel® was also indicated for treatment for the prevention of physiological lactation ("PPL") in postpartum women who either chose not to breast-feed or were medically unable to do so. In 1983 and 1987, FDA required the drug manufacturer to add warning language in response to anecdotal reports of hypertension, seizure, myocardial infarction and stroke in postpartum women using Parlodel®. In 1988 and 1989, FDA Advisory Committees were convened to advise FDA on the use of Parlodel® for the PPL indication. The Advisory Committees did not conclude that Parlodel® was the cause of the reported adverse events, but in 1989 reported back to FDA that pharmaceutical treatment was not medically needed for the prevention of physiological lactation and accordingly recommended that the PPL indication for Parlodel® and other drugs be removed or withdrawn. Other than requesting voluntary withdrawal, FDA did not take any formal action in response to this recommendation. Parlodel® continued to be legally marketed for PPL until 1994.[22]

By 1994, the drug manufacturer was faced with an increasing risk of legal liabilities and adverse publicity (fostered in part by the regulatory record) and elected to voluntarily withdraw Parlodel®'s PPL indication. Shortly thereafter, FDA withdrew approval for Parlodel® for treatment of PPL. However, Parlodel® continued to be approved for other indications and the current FDA-approved label for Parlodel® continues to state that "a causal relationship between Parlodel® (bromocriptine mesylate) administration and hypertension, seizures, strokes, and myocardial infarction in postpartum women has not been established."[23]

Notwithstanding the labeled disclaimer, the regulatory history of Parlodel® helped fuel the filing of products liability claims across the country. However, in these cases, the courts have gotten it right. In 2001, the U.S Court of Appeals for the Eighth Circuit in *Glastetter v. Novartis Pharmaceuticals Corp.* drew a clear line between FDA regulatory action and scientifically reliable evidence of causation:

> The FDA evaluates pharmaceutical drugs using a different standard than the causation standard at issue in the present case. . . . In effect, the FDA balanced Parlodel's possible harm against its limited benefit. Such balancing is irrelevant in determining the threshold question posed in this appeal: whether Glastetter's experts properly "ruled in" Parlodel as a cause of [intracerebral hemorrhages].
>
> The FDA's approach differs from ours in another critical aspect. The FDA will remove drugs from the marketplace upon a lesser showing of harm to the public than the preponderance-of-the-evidence or more-likely-than-not standards used to assess tort liability. The methodology employed by a government agency results from the preventive perspective that the agencies adopt in order to reduce public exposure to harmful substances.[24]

The following year, the Tenth and Eleventh Circuits followed suit in similarly affirming *Daubert* exclusions of plaintiffs' experts in Parlodel® litigation. In *Hollander v. Sandoz Pharmaceuticals Corp.*, the Tenth Circuit agreed with *Glastetter*, finding that FDA's "differing standards militate against applying regulatory actions to the elements of tort law . . . because "the agencies' threshold of proof is reasonably lower than that appropriate in tort law."[25] In *Rider v. Sandoz Pharmaceuticals Corp.*, the Eleventh Circuit likewise noted that the risk-utility analysis applied by FDA "involves a much lower standard than that which is demanded by a court of law. A regulatory agency such as the FDA may choose to err on the side of caution. Courts, however, are required by the

Daubert trilogy to engage in objective review of the evidence to determine whether it has sufficient scientific basis to be considered reliable."[26] District courts in the Third, Fourth, and Seventh Circuit have reached the same conclusion in response to similar Parlodel® claims.[27]

The Parlodel® litigation has provided FDA with a powerful tool to wrest control of its regulatory actions back from the plaintiff bar and, over the past year, FDA has adopted the Parlodel® court's analysis as official FDA policy. FDA first cited *Glastetter* and the district court opinion in *Hollander* in its Dec. 6, 2002 announcement of final rule-making with regard to the labeling of over-the-counter antiemetic, antihistamine, antitussive, and nighttime sleep aid products containing diphenhydramine citrate or diphenhydramine hydrochloride. In announcing labeling changes warning against the concurrent use of two or more such products, FDA made clear that the warning should not be interpreted as a finding that such use had been reliably linked to adverse events:

> FDA's decision to act in an instance such as this one need not meet the standard of proof required to prevail in a private tort action. (*Glastetter v. Novartis Pharmaceuticals Corp.*, 252 F.3d 986, 991 [8th Cir. 2001]). To mandate a warning or take similar regulatory action, FDA need not show, nor do we allege, actual causation.
>
> > "The distinction between avoidance of risk through regulation and compensation for injuries after the fact is a fundamental one. In the former, risk assessments may lead to control of a toxic substance even though the probability of harm to any individual is small and the studies necessary to assess the risk are incomplete; society as a whole is willing to pay the price as a matter of policy. In the latter, a far higher probability (greater than 50%) is required since the law believes it is unfair to require an individual to pay for another's tragedy unless it is shown that it is more likely than not that he caused it. . . ."
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> *In re "Agent Orange" Product Liability* Litigation, 597 F. Supp. 740, 781 (E.D.N.Y. 1984), *aff'd*, 818 F. 2d 145 (2d Cir. 1987). In making its decision, the agency follows "the preventive perspective that [ ] agencies adopt in order to reduce public exposure to harmful substances." *Glastetter*, 252 F.3d at 991, (quoting *Hollander v. Sandoz Pharmaceuticals Corp.*, 95 F. Supp. 2d 1230, 1234 n. 9 (W.D. Okla. 2000)). That is what we have done here.[28]

Over the ensuing 10 months, up to the date of the drafting of this article, FDA has cited *Glastetter* for this same proposition with regard to labeling decision regarding at least five additional groups of OTC drug products.[29] In addition, on July 11, 2003, FDA again quoted from *Glastetter* in explaining its decision to require that trans fatty acids be declared in the nutritional label of conventional foods and dietary supplements, making clear that its labeling decision should not be interpreted as a scientific conclusion that trans fatty acids consumed at ordinary intake levels from foods actually cause congestive heart failure.[30] While FDA does not routinely announce labeling decisions regarding prescription drugs in the federal register, it is reasonable to assume that FDA likewise has adopted *Glastetter* as its official position in the prescription drug context as well.

FDA's statement of position regarding the meaning of its regulatory action is entitled to deference and should carry significant weight in prescription drug litigation. If it does carry such weight, FDA (and the Parlodel® courts) will have taken a significant step towards a more reasoned and effective regulatory regime for prescription drugs and will have imposed a needed check on the improper "piling on" tactics of the plaintiff bar in tort litigation.

Conclusion

FDA's ability to achieve it dual objectives of ensuring the availability of new pharmaceutical products while protecting the public against undue health risks has been significantly impeded in recent years by the tort plaintiff bar's ability to distort FDA regulatory action into official "findings" of causation. In the Parlodel® litigation, the defendants successfully blocked this tactic. FDA's adoption of the Parlodel® courts' analyses as official agency position provides drug manufacturers with an important new tool in defending against such tactics in the future.

ENDNOTES

1. Speech Before Physician Insurers of America, Remarks by Mark B. McClellan, MD, PhD, Commissioner, Food and Drug Administration (May 24, 2003), at 4, *reprinted at* www.fda.gov/ocospeeches/2003 (hereinafter "McClellan PIA Speech, at ___").

2. DiMasi JA, *et al.*, *The price of innovation: new estimates of drug development costs*, J. Health Economics (2003) 22; 151-185.

3. Brief Description with Caveats of System, Surveillance and Data Processing Branch of the Division of Epidemiology and Surveillance, Division of Epidemiology & Surveillance, Dec. 1988 at 1 ("1988 FDA Caveats at ___"); *see also* Brief Description with Caveats of System (11/91), Adverse Reactions Reporting System, Division of Epidemiology & Surveillance, Surveillance and Data Processing Branch, Nov. 1991, at 1 ("1991 FDA Caveats at ___").

4. 1988 FDA Caveats at 1.

5. 1988 FDA Caveats at 2; *see also* 1991 FDA Caveats at 2.

6. Final Rule, Department of Health and Human Services, Food and Drug Administration, "Postmarketing Expedited Adverse Experience Reporting for Human Drug and Licensed Biological Products; Increased Frequency Reports," 62 Fed. Reg. 34166, 34167 (1997) (to be codified at 21 C.F.R. §§ 310, 314, and 600).

7. *See* Safety Requirements for Human Drug and Biological Products (Proposed Rule), 68 Fed. Reg. 12,406 (March 14, 2003) ("FDA Proposed Rule at ___").

8. *Id.* at 12,417.

9. *Id.*

10. *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 348 (2001).

11. Food and Drug Administration Modernization Act of 1997, S. Rep. 105-43 (1997) (discussing 1997 amendment to FDCA.

12. *See Amicus* Brief for the United States, *Motus v. Pfizer, Inc.*, Nos. 02-55372 & 02-55498 (9th Cir. Sept. 19, 2002) (on file with author).

13. FDA Proposed Rule at 12,418. In response to this concern, FDA suggests that perhaps the agency should consider also "prohibiting use of SADR reports the agency receives in product liability actions." *Id.* at 12,419.

14. *See Amicus* Brief for the United States, *Dowhal v. SmithKline Beecham Consumer Health Care, LP*, No. A094460, at 4 (Cal. App. 1st Dist. March 25, 2002) (on file with author).

15. McClellan PIA Speech, at 5.

16. Speech Before the Commonwealth Club, San Francisco, California, Remarks by Mark B. McClellan, MD, PhD, Commissioner, Food and Drug Administration (June 9, 2003), at 3-4, *reprinted at* www.fda.gov/ocospeeches/2003.

17. McClellan PIA Speech, at 5.

18. *Id.* at 3-4.

19. *Id.* at 4-5.

20. *Id.* at 5.

21. *Rider v. Sandoz Pharms. Corp.*, 295 F.3d 1194, *petition for reh'g and reh'g en banc denied* (11th Cir. Aug. 19, 2002), *aff'g Siharath v. Sandoz Pharms. Corp.*, 131 F. Supp. 2d 1347 (N.D. Ga. 2001); *Hollander v. Sandoz Pharms. Corp.*, 289 F.3d 1193 (10th Cir.), *cert. denied*, 123 S. Ct. 697 (2002), *aff'g* 95 F. Supp. 2d 1230 (W.D. Okla. 2000); *Glastetter v. Novartis Pharms. Corp.*, 252 F.3d 986, *petition for reh'g and reh'g en banc denied* (8th Cir. July 13, 2001), *aff'g* 107 F. Supp. 2d 1015 (E.D. Mo. 2000); *Dunn v. Sandoz Pharms. Corp.*, ___ F. Supp. 2d ___, 2003 WL 21856420 (M.D.N.C. Aug 4, 2003); *Soldo v. Sandoz Pharms. Corp.*, 244 F. Supp.2d 434 (2003); *Caraker v. Sandoz Pharms. Corp.*, 188 F. Supp. 2d 1026 (N.D. Ill. 2001) (no appeal); *Brumbaugh v. Sandoz Pharms. Corp.*, 77 F. Supp. 2d 1153 (D. Mont. 1999) (no appeal); *Revels v. Novartis Pharms. Corp.*, No. 03-98-00231, 1999 WL 644732 (Tex. App. Aug. 26, 1999). For further discussion of the Parlodel® *Daubert* battles, *see* Terence F. Kiely, Science and Litigation: Products Liability in Theory and Practice 177 (CRC Press 2002) (describing Parlodel® litigation as "the first significant products liability causation debate of the 21st century" and one that "will serve as a guide to understanding the significant causation issues that will continue to be involved, at increased rates of complexity, in the 21st century products cases").

22. *See Soldo*, 244 F. Supp. at 442-43.

23. *See id.* at 444-45.

24. *Glastetter*, 252 F.3d at 991 (citations omitted).

25. *Hollander*, 289 F.3d at 1215.

26. *Rider*, 295 F.3d at 1201.

27. *See Dunn*, 2003 WL 21856420, at *10 ("The FDA is concerned with safety and risk benefit analysis: if the risks outweighed the benefits, the FDA may take regulatory action. . . . The FDA's balancing does not demonstrate that Parlodel may cause stroke in postpartum women."); *Soldo*, 244 F. Supp. 2d at 513 ("FDA decision-making is based on a different standard than tort law-based scientific proof of causation."); *Caraker*, 188 F. Supp. 2d at 1040 ("Plaintiffs' experts' contention that the FDA's order directly supports their opinions ignores that the agency's determination is based on a risk-benefit analysis, a standard much lower than the one this court must now apply.").

28. *Labeling of Diphenhydramine-Containing Drug Products for Over-the-Counter Human Use*, 67 Fed. Reg. 72,555, at 72,556 (Dec. 6, 2002).

29. *Skin Protectant Drug Products for Over-the-Counter Human Use; Astringent Drug Products; Final Monograph; Proposed Rule*, 68 Fed. Reg. 35,346 (June 13, 2003); *Ingrown Toenail Relief Drug Products for Over-the-Counter Human Use*, 68 Fed. Reg. 24,347 (May 7, 2003); *Antidiarrheal Drug Prod-*

ucts for Over-the-Counter Human Use; Final Monograph, 68 Fed. Reg. 18,869 (Apr. 17, 2003); *Labeling for Oral and Rectal Over-the-Counter Drug Products Containing Aspirin and Nonaspirin Salicylates; Reye's Syndrome Warning*, 68 Fed. Reg. 18,861 (Apr. 17, 2003); *Over-the-Counter Vaginal Contraceptive Drug Products Containing Nonoxynol 9; Required Labeling*, 68 Fed. Reg. 2,254 (Jan. 16, 2003).

30. *Food Labeling: Trans Fatty Acids in Nutritional Labeling, Nutrient Content Claims, and Health Claims*, 68 Fed. Reg. 41434, at 41441 (July 11, 2003). ■

