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Merck Settles Vioxx® Litigation with State Attorneys General: an Analysis

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Executive Summary

Merck's $58 million consumer fraud settlement with 29 states and the District of Columbia affects a broad swath of pharmaceutical company activities, including advertising and promotion, continuing medical education, drug safety monitoring boards, journal authorship and clinical trial posting. It may set new enforcement standards.

Merck's recent settlement of consumer fraud claims by State Attorneys General (AGs) represents the latest and perhaps most important reminder to date that regulation of pharmaceutical company practices by the U.S. Food and Drug Administration (FDA) is only one dimension of the current regulatory and enforcement landscape. The State AGs have firmly positioned themselves as potent enforcers in their own right who have the will and the means both to extract significant financial penalties, and perhaps even more importantly, to impose significant going-forward constraints on the pharmaceutical and device industries.

Background

Nature abhors a vacuum. Experience proves that this aphorism, attributed to Aristotle in the context of what we now call thermodynamics, is equally applicable in a variety of social, political and legal contexts. In other words, as the perception has grown over the last several years that FDA is not adequately regulating pharmaceutical manufacturer conduct, including drug advertising and promotion and drug safety, other regulators and enforcers have stepped in to fill the perceived void. These enforcers have pursued actions against the industry, including, for example, civil False Claims Act actions by *qui tam* relators, U.S. Department of Justice Criminal Division prosecutions, corporate integrity agreements imposed by the Office of the Inspector General in the Department of Health and Human Services, and a multitude of State AGs claims brought in the context of "off-label" drug promotion and drug pricing. These disparate claims routinely overlap and, in some instances, encourage the private plaintiffs bar to pursue major consumer fraud and product liability class action litigation against pharmaceutical companies based upon the same set of factual allegations initially raised in the government investigations.

Perhaps even more notably, long time critics of the pharmaceutical industry in Congress, now chairing influential committees in both the U.S. House of Representatives and the U.S. Senate, have been aggressively filling the perceived gap in FDA enforcement. For example, the Subcommittee on Oversight and Investigations of the House Committee on Energy and Commerce most recently demanded that the heads of several pharmaceutical companies, as well as the Pharmaceutical Research and Manufacturers Association (PhRMA) on behalf of the industry as a whole, "voluntarily" agree to a two-year post-approval moratorium on their direct-to-consumer (DTC) advertising and otherwise commit to modifying DTC practices in ways that probably exceed Congress' authority under the First Amendment to legislate restrictions on such protected "speech."[1] The overall effect of all of these efforts is that of a "perfect storm" threatening to use litigation and subpoena power to re-shape permanently the regulatory landscape of the entire pharmaceutical industry.

State AGs, often with private plaintiff firms acting as proxies on their behalf, have been adept over the years in coordinating their efforts on a multistate basis to address what they perceive is a regulatory vacuum in Washington, D.C. They have been particularly aggressive in challenging pharmaceutical company behavior and have extracted settlements that include significant monetary penalties, as well as judicially enforceable commitments to change various practices to conform to what the State AGs decide is best. For example, the current requirements for greater transparency in clinical trial registration and posting, and the related movement toward disclosure in pharmaceutical and device company financial relationships with health care practitioners, were the result of an investigation by the New York State Attorney General's Office and subsequent settlement with a pharmaceutical manufacturer over the alleged failure to divulge negative clinical trial information. Other examples abound. But perhaps the single most significant such action and settlement to date is the recently announced settlement between Merck and a working group of attorneys general from 29 states and the District of Columbia, led by the Oregon Attorney General's Office.[2]

Even putting aside the substantial $58 million civil monetary settlement agreed to by Merck, the remedial provisions of the settlement are potentially profound. They establish enforceable requirements for a broad swath of pharmaceutical company practices that state attorneys general will likely now insist upon from all pharmaceutical manufacturers. As a practical matter, the

[1] Committee Correspondence *available at* http://energycommerce.house.gov/Press_110/110pr_oversight.shtml#Letters (May 20, 2008)
[2] Available at http://www.merck.com/newsroom/vioxx/pdf/ag_document.pdf

settlement effectively vests FDA with greater authority over DTC advertising than even FDA believes it has under its organic statute, which new authority is contractually enforceable under the settlement not by FDA directly but by the State AGs in a contempt proceeding. This "backdoor" approach to expanding FDA's authority is a clever and powerful approach that the State AGs have devised both to challenge FDA itself to be more aggressive in the agency's approach to various pharma company practices and to exercise their own muscle if FDA does not. Indeed, there is at least one other such settlement involving a company other than Merck currently being negotiated by the State AGs that will include similar forward-looking obligations. Accordingly, pharmaceutical (and device) company strategies for responding to and mitigating this perfect storm are well informed by a close examination of the terms of the Merck settlement agreement.

Terms of the Merck Settlement

The settlement resolves allegations against Merck under the consumer fraud statutes of the participating states for conduct relating to advertising and promotion of Vioxx®, as well Merck practices relating to continuing medical education, Drug Safety Monitoring Boards, journal authorship and clinical trial posting. Notably, the settlement does not resolve allegations about Merck's conduct relating to Vytorin® and Zetia®, which appear to be the subject of other ongoing investigations by the State AGs. The potential resolution of these lingering issues will provide the State AGs with yet another opportunity to add additional fencing-in provisions intended to address alleged objectionable aspects of Merck's conduct.

PROMOTIONAL CLAIMS GENERALLY

In the settlement agreement, Merck agrees both to refrain from making promotional claims, including oral statements by its sales representatives, that are false, misleading or deceptive, and to comply with the Federal Food, Drug, and Cosmetic Act (FFDCA) and FDA requirements in connection with advertising and promotion. Indeed, even though the settlement agreement was effected under the various state consumer protection statutes, it largely sidesteps the entire preemption controversy by explicitly[3] acknowledging that Merck is not required to take any action prohibited by the FFDCA or FDA, nor is it obligated to refrain from taking any action mandated by the FFDCA or FDA. But what is remarkable about the settlement is that given all of the controversy about FDA's asserted inaction in policing the pharmaceutical advertising and promotion marketplace, including alleged delays by the agency in issuing compliance correspondence, including Warning Letters, about advertising violations, the State AGs now effectively stand in the agency's shoes under the federal law provisions governing advertising and promotion, and can police the marketplace as against Merck as they deem appropriate.

The potential for conflict between FDA and the State AGs is apparent in this provision, and runs through much of the remainder of the settlement agreement as well. In other words, and to the extent that State AGs are now in the position of enforcing FDA's own standards, there is significant potential for conflict between what they believe FDA requires and how FDA itself interprets its own regulations. This may lead to an endless round of discussions with multiple regulators about the propriety of particular behavior. Moreover, by giving the State AGs the power to enforce FDA requirements, the settlement agreement may effectively eviscerate the concept of FDA enforcement discretion, which has been a bedrock principle in food and drug law enforcement since the agency's inception. The long-term impact of such a fundamental shift in enforcement authority remains to be seen.

DIRECT-TO-CONSUMER TELEVISION ADVERTISING

Post-Approval Moratorium on DTC TV Advertising

There has been significant controversy about whether and to what extent pharmaceutical companies should delay the inception of DTC television advertising after a product is first approved. There are at least two reasons offered for such a post-approval moratorium. First, it is argued that a moratorium of perhaps as long as two or three years will allow for a more gradual uptake of the new product, thereby permitting additional real world safety information to accumulate before there is massive exposure of

[3] *On preemption generally see* McDermott Will & Emery *On the Subject* "Third Circuit Decides Long-Awaited Antidepressant Drug Labeling Cases," (April 14, 2008), *available at* http://www.mwe.com/info/news/ots0408e.htm; McDermott Will & Emery *On the Subject* "Supreme Court Holds That FDA Approval of Class III Medical Device Preempts State Tort Law," (February 28, 2008), *available at* http://www.mwe.com/info/news/ots0208i.htm.

the public to the new product. Second, it is argued that a moratorium will allow physicians to become more knowledgeable about the new product before facing the increased demand from their patients occasioned by DTC television advertising. Whatever one thinks about the factual basis for these justifications, or the constitutionality under the First Amendment of a moratorium based on these justifications, momentum is building for such a restriction.

Under the settlement agreement, the State AGs have forced Merck to effectively cede to FDA control over the timetable for initiation, post-approval, of DTC television advertising for new Merck products indicated for pain relief. In other words, the agreement provides that Merck will abide by any official FDA recommendation for how long after approval Merck must wait before launching DTC television advertising for these new products. Accordingly, the legal and constitutional merits of FDA's authority to impose a post-approval delay in DTC television advertising have apparently been taken off the table by Merck's undertaking in the settlement agreement. In pursuing this approach, the State AGs appear to be gambling that FDA will actively manage the post-approval DTC moratorium process in a way consistent with their views. Members of Congress are also aggressively pushing the industry to agree voluntarily to a post-approval DTC television advertising moratorium. Both of these initiatives involve obligations that go well beyond the conceptual underpinnings of the voluntary post-approval delay of DTC television advertising that is already part of the PhRMA Guiding Principles on DTC advertising, which has to do almost exclusively with physician education about a new product before commencement of post-approval DTC.[4]

While the State AGs have forced Merck to agree to an FDA-imposed post-approval moratorium on DTC television advertising for a single class of Merck products, they are likely to pursue such terms for any product class touched by their future investigations. The context of such coercive settlements dramatically reduces the opportunity and likelihood of a constitutional challenge to a post-approval DTC moratorium.[5]

Voluntary "Prior Restraint" on DTC TV Advertising

In the PhRMA DTC Principles, industry voluntarily agreed to submit all new DTC television advertising to FDA for prior review.[6] Likewise, in the Food and Drug Administration Amendments Act of 2007 (FDAAA), Congress provided for a voluntary, user fee funded system for FDA prior review of television advertising.[7] However, neither of these obligates the submitter to wait for affirmative FDA approval before launching a new DTC advertising campaign. Indeed, and apparently over concern about the constitutionality under the First Amendment of a mandatory "prior restraint" on DTC advertising, FDAAA explicitly disclaims such FDA advance approval authority.[8] At the same time, waiting for FDA to comment on a proposed new DTC campaign, and modifying the advertising accordingly, provides a degree of comfort that the advertising is acceptable to the agency. It also provides good arguments that any ensuing state law claim challenging advertising so-reviewed and so-modified is preempted.[9]

The problem of course is that the State AGs appear to have adopted a paradigm in which the manufacturer must forego independent judgment on DTC television advertising and rely, instead, on the resource-poor FDA to complete timely reviews of proposed DTC advertising. Thus, an obligation to wait before launching a new DTC campaign effectively gives FDA a pocket veto over new advertising copy. In other words, the states have effectively imposed a contractual "prior restraint" on all new Merck DTC television advertising, at least in the pain relief category. It seems reasonable to believe that the State AGs will insist on similar conditions for other companies, including perhaps Merck itself, in pending and future investigations and, as a consequence, may well be forcing the "prior restraint" practice on the entire industry.

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[4] *Available at* http://www.phrma.org/files/DTCGuidingprinciples.pdf (Principle #6).

[5] The extent to which viable constitutional arguments can still be raised at FDA and in court in certain contexts is beyond the scope of this analysis.

[6] *Id.* (Principle #8).

[7] Pub.L. 110-85, §104. That provision of FDAAA is not being implemented at this time because Congress has failed to provide a mechanism for spending any user fees that FDA might collect under the voluntary DTC review program.

[8] 21 U.S.C. §353b(c). *See also* 21 U.S.C. §352(n).

[9] *See* Arnold I. Friede and Robert B. Nicholas, *"How the FDA Pre-Review Program Could Work: A Closer Look at Preemption In the Context of the Proposed Voluntary Pre-Review Program for DTC Advertising,"* DTC Perspectives (March 2008).

PROMOTIONAL CLAIMS ABOUT CLINICAL STUDIES

The settlement agreement comprehensively regulates the nature and extent of the substantiation required before Merck may make promotional claims in print and other media both to physicians and to consumers about the safety or effectiveness of a Merck product based on clinical studies, and how, even if substantiated, these claims must be presented to avoid them being judged misleading. These provisions largely mirror FDA's existing prescription drug advertising regulations on the subject.[10] Hence, and while the underlying obligations themselves are not novel, the fact that State AGs, individually and collectively, can now march into court under FDA's own regulations effectively means that there is a "new cop on the beat" ready, willing and able to pursue actions for alleged advertising violations whenever they believe FDA is not doing the job properly.

CONTINUING MEDICAL EDUCATION (CME) AND CONFLICTS OF INTEREST

The settlement agreement addresses CME in a number of significant respects.[11] Taken together, the CME provisions of the settlement agreement create new, more stringent conflict of interest standards for CME presenters.

First, the settlement agreement incorporates by reference and attaches the Standards for Commercial Support adopted by the Accreditation Council for Continuing Medical Education (ACCME) and extracts a promise from Merck to comply with these, which virtually all large pharma companies are doing now anyway. Second, it goes beyond the ACCME standards by addressing potential conflicts of interest created by participation as CME speakers of individuals who have a "promotional relationship" with Merck. Merck is now obligated to include provisions in its contracts with promotional speakers that requires those who have had a promotional relationship with Merck over the course of any preceding 12-month period to divulge to CME providers, for inclusion in the written program materials, and to divulge orally to attendees at CME meetings, the specific existence, nature and purpose of the promotional relationship with Merck. This requirement applies if the CME program involves a product in the same therapeutic category as the one for which a promotional relationship exists. Moreover, the settlement agreement prohibits Merck from funding any CME program if it knows that a speaker at the CME event has been a promotional speaker for Merck relating to the class of drugs to be discussed at the CME program during the preceding 12 months.

Clearly, these terms are highly intrusive and potentially counter-productive. While they may serve the State AGs' apparent goal of addressing the potentially biasing influence of industry relationships, this preclusion may well deter significant numbers of physicians, including some who are probably the most interested and qualified to participate as CME speakers, from engaging in promotional relationships with pharmaceutical companies or, alternatively, from participating in CME altogether. Either result seems unfortunate, as it may well remove some of the most qualified individuals from participation in one or another of these important activities.

DRUG SAFETY MONITORING BOARDS AND CONFLICTS OF INTEREST

In the course of the investigation, the State AGs became concerned about what they saw as at least one major financial conflict of interest on the external Drug Safety Monitoring Board (DSMB) that reviewed the results of the VIGOR trial for Vioxx® in 1999 but that failed to stop the trial thereby allowing the drug to reach the market.[12] Whatever the actual merits of the conflict of interest claim, this perception by the State AGs led to comprehensive standards in the settlement agreement governing financial conflicts of interest for members of external DSMBs reviewing Merck safety studies. The standards imposed on Merck appear to go well beyond current industry practice. They include prohibitions against: (a) service as a DSMB member by anyone who holds in excess of $25,000 worth of Merck stock; (b) trading in Merck stock during service as a DSMB member; (c) service as a DSMB member by anyone who serves as a clinical trial investigator in the study being monitored; and (d) consulting for, being employed by or entering into future consulting or employment arrangements with Merck while serving on a Merck DSMB, except that an individual may simultaneously serve on more than one Merck DSMB, and may do "non-promotional" consulting for Merck's research arm but only for compensation that does not exceed $15,000 annually in the aggregate.

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[10] *See e.g.* 21 CFR §202.1(e)(7).

[11] There has been much controversy about the nature and extent of industry support for CME and the potential biasing influence of such support. Indeed, a recent draft report from the Council on Ethical and Judicial Affairs of the American Medical Association makes the largely unsupported recommendation that all industry funding of all CME should be ended. *Available at* http://www.ama-assn.org/ama1/pub/upload/mm/471/ceja1.doc.

[12] *See e.g.* Snigdha Prakash, *"Conflicted Safety Panel Let Vioxx Study Continue,"* National Public Radio, *"All Things Considered"* (June 8, 2006), available at http://www.npr.org/templates/story/story.php?storyId=5462419

Of note is the fact that the settlement agreement goes beyond mere financial conflicts and also addresses the much murkier world of other kinds of potentially biasing conflicts of interest among DSMB members. For example, the agreement requires that all prospective DSMB members divulge on a "competing interest" form, and update on an ongoing basis, information about (a) consulting or frequent speaking engagements for Merck; (b) career involvement with the product or technique under study; (c) hands-on participation in the trial; (d) emotional involvement in the trial; (e) intellectual conflicts; (f) involvement in regulatory issues relevant to trial procedures; (g) investment in competing products; and (h) involvement in the publication of the trial results. This information must be submitted to the DSMB chair who in turn will forward it to the chair of the study's Steering Committee for review and action before the first DSMB meeting and on an ongoing basis. Given vague standards like "intellectual conflict" or "career involvement" with the product under study, it may well be, again, that the most qualified individuals will be categorically disqualified from participation on DSMBs or from service in other areas of substantial importance to the public health. One can certainly question the wisdom of such a result.

AUTHORSHIP AND CONTRIBUTION

The settlement agreement requires that anyone named as an author on a Merck-sponsored manuscript for a Merck-sponsored study must first fulfill a number of conditions. These include: (a) having made a substantial contribution to the conception and design or acquisition of data, or analysis and interpretation of data; (b) having involvement in drafting the article or revising it critically for important intellectual content; and (c) having possession of final approval rights over the version to be published. Moreover, in cases where a large multi-center group has conducted the research, the manuscript should identify the individuals who accept direct responsibility, and each of them must satisfy the foregoing authorship standards.

These requirements address the controversy that has evolved over what is sometimes euphemistically called "ghostwriting" and the nature and extent of a contribution that a named author must make to be listed as such on a published scientific manuscript. The International Committee of Medical Journal Editors has adopted "Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication,"[13] which the settlement agreement appears to have adopted *in toto*. Thus, a failure on Merck's part to adhere to these requirements now also amounts to a violation of the settlement agreement.

CLINICAL TRIAL POSTING

The settlement obligates Merck to register and submit clinical trial results to the clinical trial registry and results data bank created by FDAAA.[14] This obligation applies retroactively to "applicable clinical trials" as defined in FDAAA[15] initiated by Merck after June 1, 2005. While the new FDAAA clinical trial transparency requirements are subject to enforcement by FDA, the settlement provisions on the subject now also give each of the participating State AGs the contractual right to commence an action for contempt of court if Merck fails to comply with its new federal law clinical trial posting obligations. This theme about the states' ability to enforce federal law requirements pervades the settlement agreement and reflects the states' uncertainty if not outright distrust of FDA's ability and willingness to act as a vigorous enforcer in this area.

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[13] *Available at* http://www.icmje.org/#author (October 2007).

[14] *See* McDermott Will & Emery *On the Subject* "FDA Issues Draft Guidance on Certification Requirements Under New Clinical Trial Registration and Posting Requirements," (April 29, 2008), *available at* http://www.mwe.com/info/news/ots0408r.htm.

[15] *See id.*

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