Trends in Prosecutions and So-called Off-label Promotion Issues

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The views expressed here are my own personal views.

Off Label Promotion: In General

- Physician prescription of a product off-label is lawful
- Drug/Device company must obtain FDA approval to sell drug/device (approval depends on classification):
  - Must demonstrate drug/device is safe and effective for intended use
  - Drug/device must contain labeling reflecting, among other things, conditions of use

Labeling Is Critical

- Prior to approval, FDA reviews
  - Proposed labeling: what mfgr is claiming to the intended user
  - Specifics about risks and benefits;
  - Results of animal, pre-clinical and clinical trials
  - Evidence regarding safety and efficacy. 21 CFR 201.100(d).

Intended Use: 21 CFR 201.128

- The intent is determined by such persons' expressions or may be shown by the circumstances surrounding the distribution of the article. This objective intent may, for example, be shown by labeling claims, advertising matter, or oral or writt statements by such persons or their representatives It may be shown by the circumstances that the article is, with the knowledge of such persons or their representatives, offered and used for a purpos for which it is neither labeled nor advertised.

Intended Use

- But if a manufacturer knows, or has knowledge of facts that would give him notice that a device introduced into interstate commerce by him is to be used for conditions, purposes, or uses other than the ones for which he offers it, he is required to provide adequate labeling for such a device which accords with such other uses to which the article is to be put.

Post Approval

- Claims in promotional "labeling" or advertising must be consistent with approved labeling. 21 C.F.R. 202.1(e)(4).
- Issues arise regarding:
  - dissemination of reprints of articles
  - Continuing medical education programs
  - Sales and marketing brochures, statements

Relevant Factors

- What is the total marketplace for the approved uses?
- Does marketing target doctors who do **not** treat persons with the intended medical issues?
  - Does it have sales budgets for non-approved uses?
  - Are employees paid bonuses for sales for non-approved uses?
- Did company seek FDA approval for other uses and not get it?

Relevant Factors

- Did the company choose not to seek FDA approval? Why not?
  - To protect a future drug from generic competition?
  - No data to demonstrate product is safe and effective?
- If company is using literature to support unapproved uses, does it claim the product is safe and effective for those uses?
- Does it employ consultants to push off label?
- Does it incent customers to prescribe off label?

Free Speech v. Off-Label Promotion

- No free speech right to promote a device for an off-label use
  - There is a tension between the "exchange of reliable scientific data and information within the health care community and the statutory requirements that prohibit companies from promoting products for unapproved uses."
    - Virginia Bd. Of Pharmacy v. Virginia Citizens Consumer Counil, inc., 425 U.S. 748, 765 (1976).

Off-Label Promotion

- Government has a substantial interest in the regulation of medical devices and in "subjecting off-label uses to the FDA's evaluation process."
- "[P]ermitting defendants to engage in *all* forms of truthful, non-misleading promotion of off-label uses would severly frustrate the FDA's ability to evaluate the effectiveness of off-label uses."
  - United States v. Caputo, 288 F. Supp. 2d 912 (N.D.Ill. 2003).

Lessons Learned

- Monitor development of off-label sales
- Scrutinize incentive programs for risk that sales force will be pushing off-label uses
- Conduct compliance audits of sales force activities
- Evaluate marketing and promotional campaigns against the directions for use

Resolutions > $1,000,000 (305)

Four year Period Ending	Total Amount Recovered	Criminal Fines	Settlements Less than $10,000,000	Settlements More than $99,999,999
12/31/1994	$602,000,000	$97,300,000	1	2
12/31/1998	$1,676,837,748	$93,600,000	21	7
12/31/2002	$4,642,527,772	$603,593,600	45	7
12/31/2006	$8,218,577,264	$956,147,866	96	18

Total: $15,866,250,180; criminal fine: $1,770,821,466

Source: Loucks and Lam, *Prosecuting and Defending Health Care Fraud Cases, 2007 Cumulative Supplement, Chapter 11 (BNABooks.com) (due out in December).*

Drug Industry Cases

Years	Total Recoveries	Pharma Cases	%
1991-1995	856,600,000	171,000,000	19.9
1996-2000	3,602,040,776	274,440,776	7.6
2001-August 2006	9,362,622,955	5,388,666,004	57.6
Totals	13,821,263,731	5,834,106,780	42.2

Source: Loucks and Lam, *Prosecuting and Defending Health Care Fraud Cases, 2006 Cumulative Supplement, Chapter 11 (BNABooks.com); settlements in excess of $10,000,000 only*

Mix: by dollars

- **42.2 %: pharmaceutical products**
- 26.8 %: hospitals
- 6.8 %: dialysis providers
- 6.1 %: laboratories
- 3.7 %: carriers/intermediaries
- 3.5 %: nursing homes
- 3.3 %: medical devices

Source: Loucks and Lam, *Prosecuting and Defending Health Care Fraud Cases, 2006 Cumulative Supplement, Chapter 11 (BNABooks).*

Sentencing, Schering Sales Corporation, Comments by the Court, 1/17/2007

"[I]t's been upsetting to me how many of the big pharmaceutical companies have engaged in what I view as clearly illegal behavior in terms of off-label marketing.

I've seen lots of other stuff that I'm not bringing into this particular case, but on the off-label marketing, it is against the law to market if it's not an FDA-approved indication. I do not accept that there is a First Amendment right to market something that does not get FDA approval.

Comments by Judge Saris, cont.

But if it's ever been unclear, to Schering or anyone else, you cannot market for indications that the FDA has not approved or has rejected. It can't happen. And I saw it with Neurontin, and I saw it here. I mean, the enormous frustration I have felt having seen so much of this is, once it ends up in the civil fraud arena, all the issues that I tried to work through in the restitution come to the front. And how do you prove the nexus? How do you prove that it's based on the fraudulent marketing?

Comments by Judge Saris, cont.

And I think the pharmaceutical companies take advantage of this. They know, just based on aggregate marketing data, that they bump up or boost up the sales. But in a civil case, it can take you five years to unravel this stuff; and if I could have found an appropriate vehicle to have ordered restitution to the third-party payors, I would have done it.

Comments by Judge Saris, cont.

The thing that's so upsetting to me is, it wasn't just the Claritin, but it was people with brain cancer and serious illnesses. And this isn't the only company. It just almost seems as if the pharmaceutical companies said, "Yeah, yeah, yeah" to the FDA and then went and did it anyway.

Comments by Judge Saris, cont.

[W]hy buy the cow when you can get the milk for free? And that's even much better put. So the question is, you can't thumb your nose at the FDA. Maybe it's too slow sometimes. Maybe it's in some ways not aggressive enough in enforcing its own rules sometimes, but at the end of the day, you can't market off-label. So I don't know how further to send this message if other people from the industry are listening and watching, but it's wrong. And I think that this is a stiff fine and an appropriate civil settlement.

Litigation Risk: Class Actions

- Federal Prosecution of Parke Davis for off-label promotion of Neurontin, resolved May 2004: $430,000,000 payment
- Follow on litigation still pending, September 2007, federal court in Boston:
  - In re Neurontin Marketing and Sale Practices, 2007 WL 2437954

August 29, 2007 Opinion

- One calendar quarter after the campaign to publicize Neurontin for pain started, Neurontin prescriptions for pain increased 2500%.
- Within three months after the migraine promotion commenced … usage increased 800%.
- After the psychiatric off-label campaign began, psychiatric use increased 1000% in [6]months.
- Evidence demonstrates that off-label prescriptions of Neurontin amounted to approximately 13% of total scripts prior to the off-label promotional campaign.
- Off-label prescriptions constituted 90% of total scripts at the end of the class period.

Co: Ignore our marketing

- Company's argument: ignore our marketing effort:
  - "surge in off-label prescriptions could be explained by advances in medical knowledge, through "postings on medical websites, advances in basic science, and informal conversations" which create a buzz about the drug."
- The Court: Pfizer believes its promotional campaign has an impact because it spends so much time and money on marketing and evaluating its effect.
  - … Pfizer spends approximately $100 million annually to obtain data for use in its own marketing analyses.

Issues of Proof

- This case is troublesome because defendants allegedly used a national marketing scheme to promote a fraud.
- If true, they should not get off scot-free if there is a practical statistical way to address the difficult causation issues. [The expert's] model can prove what the effect of any fraudulent promotional campaign for an off-label indication was. If only a de minimis number of doctors prescribed Neurontin for an off-label condition, and then off-label prescriptions skyrocketed after a fraudulent campaign for that indication (i.e., migraines or bipolar), the Court will consider statistical proof as sufficient to demonstrate that most purchasers in that period were injured.

As part of his punishment for manufacturing and selling an unapproved catheter, an Alabama device wholesaler must attend 24 hours of edu
eral judge **Karon O. Bowdre** included this plea agreement provision in sentencing the wholesaler to pay a $2,000 fine, probation for one yea
marketing of a cholangiography catheter in 2005 without obtaining FDA approval. **James Lee**, 62, Birmingham, AL, pleaded guilty to two m
s founded in 1977, has three employees and sells durable medical equipment as a wholesaler.

Sentence Imposed November 2, 2007

- As part of his punishment for manufacturing and selling an unapproved catheter, an Alabama device wholesaler James Lee, 62, must attend 24 hours of educational instruction wearing a shirt reading: "I was convicted of violating the FDCA."
- Northern District of Alabama federal judge **Karon O. Bowdre** included this plea agreement provision in sentencing a wholesaler for the manufacture and marketing of a cholangiography catheter in 2005 without obtaining FDA approval.

Doing it Right

- Pressures from:
  - Competitors on pricing, quality
  - Customers on service, delivery, pricing
  - QC on following the processes
  - Regulatory affairs on following the rules
- What happens:
  - Cutting of corners
  - Sloppiness, rushing can become criminal
- Growing culture of acceptance

C.R. Bard, Inc.

- Violations of the Food, Drug and Cosmetic Act in the distribution of adulterated heart catheters
  - Several different Class III devices
  - One device suffered a failure as a result of a use that was off-label : 2 cm tip broke off
  - Company made changes in devices after approval, without seeking new approvals from the FDA

Bard

- Criminal conduct: 1987-1990
- Company charged October 1993; pled guilty and was sentenced, April 1994, fined $30,500,000, which was then the highest criminal fine ever imposed in an FDCA case
- Two month, highly publicized jury trial of employees in Boston Federal Court, summer 1995

Bard

- Restriction in labeling: affected use
- Bard was marketplace leader (55% +)
- Following the rules = loss of sales
- Marketing pamphlets, handouts, sales rep statements: all pushed off-label use
- Sales force, while aware of the label, not told the reason for restriction
- Doctors followed promotion, used device off-label

Bard

- The labeling provided to the FDA stated "Warning: Do Not Turn the Probe II device more than one rotation (360 degrees) in the same direction."
- In fact, physicians were routinely being told by USCI personnel in the human clinicals that the device could be rotated 15 times.

Bard

- First Objective: to verify that the Probe B design may be freely rotated and/or define when rotation compromises performance.

- Dr. King was anxious to use the redesigned probe in this case and checked with me several times to be sure... we could turn it ten revolutions in one direction.

Bard

- ISSUE: We have recently had several Probe failures involving the loss of the spring tip (New Probe) and/or loss of the entire neck extension (2 Regular probes).
- Physicians have been told "You can twist this thing 15 times and nothing will happen."
- We need to consider the risks, engineering evaluations, market release and training issues before this product hits the market.

Bard

- The issue that we have been struggling with is how to remain committed to that precept [quality product] when we face the daily struggle of meeting sales objectives in a highly competitive environment. I agree that we have slipped. I concur that several of the decisions including the Mini, 3 Lumen and Probe were weighted too heavily with commercial interest.

- Memo by President of the catheter division to his boss

Bard

- The USCI culture was "not keeping corporate in New Jersey totally informed about what was going on."
- "Cutting corners became a way of life. That became a way of life. Or, we'll do the testing on human beings. None of us in this room would want to be the person tested on. We cut corners which were bad. We knew things were happening and we didn't tell corporate."

Bard

- [W]e never give our people enough time to accomplish their jobs but rather rush the program to the next step before it is ready. .. We feel enormous pressure from upper management and marketing to continue despite the unsolved technical issue. .. We chose not to address these design flaws but rather to begin production and fix these things on the way. We now find ourselves in the most uncomfortable position of trying to decide what to sell without adequate tests in place to identify the quality of our results. ... Test protocol: how was this missed? Were we so with the program that we failed to anticipate that something could go wrong? Does asking tough questions or making waves put one in the political shithouse?

Lessons learned

- Are the normal processes being followed?
- Are there pressures to increase productivity, output, sales that are unrealistic for the resources available?
- Are employees being told to stay in compliance and to meet production/sales demands that are not realistic for the resources at hand, or in light of the rules governing either production or sales?
- Has someone offered a novel or new or suddenly discovered justification?
- Are there budgets with few controls that can be used to provide incentives to customers?
- Is a manager ignoring warnings from subordinates?