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The Door Opens for Off-Label Marketing: Implications for Clinical Research

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Marketing a drug, medical device, or diagnostic ("product") in the United States requires approval by the Food & Drug Administration (FDA). FDA approvals have been limited to the specific indications and populations for which clinical studies have demonstrated safety and efficacy. While physicians may prescribe products outside these FDA-approved indications and populations, companies have not been permitted to promote products for such "off label" uses. Companies violating these requirements have paid multibillion-dollar fines.[1]

Conducting the clinical research to satisfy the FDA's requirements for a new indication or population can cost many millions of dollars. However, court rulings over the past few years have opened the door for companies to promote products for off-label uses, provided the marketing employs information that is "truthful and not misleading." As a result, FDA requirements for rigorous testing to expand a product's label might no longer be required to market a product.

These rulings will have two conflicting impacts on the clinical research enterprise:

- The number of new studies to expand labels should increase dramatically.
- The number of new studies to *support FDA approval* to expand labels might decline.

On balance, the number of clinical studies to support label expansion should increase significantly, since such studies can lead to new revenue relatively quickly and inexpensively. Once a product is generating revenue for a new indication or population, the company might want to conduct the clinical trials necessary to obtain the FDA's official stamp of approval.

Background and Analysis

The U.S. Supreme Court implicitly and other federal courts explicitly have recently weighed in on whether the FDA has the authority to prevent companies from marketing a medical product for an off-label indication if the information is "truthful and not misleading." Previous court decisions go back to Central Hudson v Public Service Commission in 1980, but decisions in the last five years have had the most impact on off-label promotion.

The 2011 IMS v Sorrell case before the Supreme Court started the most recent salvo of attacks against the FDA's regulation of off-label speech.[1] While the case involved the disclosure of information regarding drug prescribing, the court opined in general on "protected speech." The Court held that, to "sustain the targeted, content-based burden…[imposed] on protected expression, the State must show at least that the statute directly advances a substantial governmental interest and that the measure is drawn to achieve that interest." The government was unable to meet its burden in this case.

Then, in 2012, in light of IMS v Sorrell, the FDA and DOJ were unable to convince the Second Circuit Court of Appeals that its prosecution of Alfred Coronia, a pharmaceutical sales representative, for his off-label promotion of a drug should be upheld.[2]

The DOJ and FDA understood the Second Circuit's holding in the Coronia case to apply to a very specific set of circumstances. However, in Amarin v FDA, the Second Circuit, in August 2015, specifically referring to the Coronia case, rejected the FDA/DOJ's narrow understanding of that case.

Based on industry successes in the Amarin and Coronia cases, Pacira Pharmaceuticals sued the FDA in the Second Circuit on similar, First Amendment grounds on September 8, 2015.[3] This case potentially takes the next step in challenging the FDA's authority over off-label promotion and its position on the sufficiency of evidence required to make promotional claims. Pacira seeks to further broaden its rights to commercial speech to include making specific claims of use, even if only broad claims of the intended use were specifically approved.

In summary, the IMS v. Sorrell decision by the Supreme Court in 2011, and the Coronia decision and Amarin decision[4] in December, 2012 and August, 2015, respectively, by the Second Circuit, among other rulings, all suggest that the courts believe that it is constitutionally impermissible for the FDA to prohibit medical product companies from discussing indications of a drug if it meets the constitutionally permissible standard. In other words, companies are now free to publicize data that supports the use of a product for a new indication or population, provided such data is "truthful and not misleading."

Limits

The FDA already permits medical liaisons, such as physicians, pharmacists and PhD scientists, to discuss off-label clinical research with clinicians, so it is not entirely opposed to off-label speech.

The court's rulings supporting the off-label promotion of a drug or device have primarily come out of the Second circuit, although decisions from the Supreme Court and the Ninth Circuit support such a holding. Accordingly, while it is likely that these decisions represent the view all federal courts, it is always possible that a different circuit court might interpret the rules differently and create a "circuit split."

Companies still need to submit clinical trials to the FDA for approval. And, of course, U.S. courts do not govern product marketing outside the U.S.

A few case studies will likely not meet the FDA's standard for "truthful and not misleading." At the opposite extreme, two or more appropriately powered, prospective, randomized, controlled, double-blinded, multi-center studies will likely meet the FDA's expectations for "truthful and not misleading" information. There is a significant gray zone between these two extremes. Accordingly, without additional clarification from the FDA, off-label marketing is still susceptible to legal and regulatory sanctions. The FDA has announced that it is working on an off-label guidance to clarify its expectations.[5]

When some patients are inevitably injured in an expanded use, any resulting litigation is likely to address the question as to whether the information that supported the expansion was, in fact, "truthful and not misleading." When an FDA-approved drug is withdrawn from the market, can one conclude that the clinical studies supporting the approval, however well designed and conducted, were, in fact, "misleading"? How convincing will that clinical study look in hindsight?

Conclusion

The FDA and Department of Justice (DOJ) are well aware of the potential impact of these rulings. According to some commentators, the Amarin and Coronia decisions are already expected to affect multibillion-dollar settlements the government seeks to obtain from companies, and possibly past settlements, as well.[6,7] A court victory for Pacira in the Second Circuit will reinforce this conclusion, but the issue might return to the Supreme Court for final adjudication.

These court decisions have opened the door to much faster and more economical expansion of medical product promotion for new indications and populations. The new "truthful and not misleading" standard still requires clarification, which might be provided by a planned FDA guidance and further litigation. However, any company that is confident in its data, perhaps because it has already been filed with the FDA, might consider taking advantage of its First Amendment rights.

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