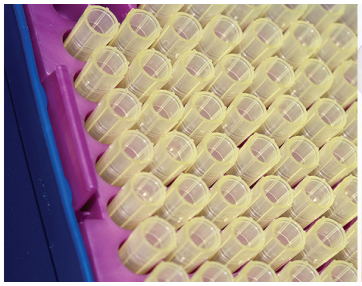




BATES WHITE
ECONOMIC CONSULTING

Empirical analysis of causation and damages in off-label marketing cases

Eric M. Gaier, Benjamin Scher, and Arun Sharma

April 2013

Eric Gaier is a Partner and Benjamin Scher and Arun Sharma are Principals in the Antitrust & Competition and Healthcare & Life Sciences practices at Bates White Economic Consulting.

Empirical analysis of causation and damages in off-label marketing cases

Eric M. Gaier, Benjamin Scher, and Arun Sharma

In recent years, the volume and scope of government investigations and *qui tam relator* complaints concerning alleged "off-label" marketing by pharmaceutical, biological, and medical device manufacturers has skyrocketed. Typically pursued under the federal False Claims Act (FCA), such investigations can give rise to substantial liability for manufacturers in the form of treble damages and civil penalties. For example, between 2004 and 2010, the U.S. government collected approximately $7.9 billion from 21 settlements related to off-label drug marketing, with more than one-half of these settlements surpassing $100 million.[1] Moreover, the government's focus on investigating off-label drug marketing shows no sign of slowing, as there were more than $2 billion in settlements and judgments related to pharmaceutical FCA matters in 2011, many involving allegations of off-label marketing .[2]

Off-label marketing refers to the practice of promoting a pharmaceutical, biological, or medical device product for an indication not explicitly approved by the Food and Drug Administration (FDA) and described on the product label. With the exception of certain safe harbors, the FDA has challenged off-label marketing as prohibited under the Federal Food, Drug, and Cosmetics Act (FDCA).[3] Importantly, however, the FDCA does not prohibit, and the FDA is not authorized to regulate, off-label prescribing by physicians. Indeed, off-label prescribing is prevalent among physicians and is often considered beneficial for patients. For example, a study based on 2001 data found that approximately 21% of all prescriptions studied involved off-label indications.[4] The same study found

---

1. Antonia F. Giuliana, "Statistics For Off-Label Marketing Settlements Involving Prescription Drugs," *FCA Alert*, Kelley, Drye & Warren, LLP, Mar. 2, 2011, *available at* http://www.fcaalert.com/2011/03/articles/settlements-1/statistics-for-offlabel-marketing-settlements-involving-prescription-drugs/.
2. U.S. Department of Justice, "Justice Department Recovers $3 Billion in False Claims Act Cases in Fiscal Year 2011," press release, Dec. 19, 2011, *available at* http://www.justice.gov/opa/pr/2011/December/11-civ-1665.html.
3. Department of Health and Human Services, Food and Drug Administration, *Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices*, Jan. 2009, *available at* http://www.fda.gov/regulatoryinformation/guidances/ucm125126.htm. In December, 2012, the United States Court of Appeals for the Second Circuit issued a ruling in *United States v. Caronia* stating, "we construe the FDCA as not criminalizing the simple promotion of a drug's off-label use because such a construction would raise First Amendment concerns." However, it remains to be seen whether, and to what extent, this ruling will have an impact on future prosecution of off-label marketing cases.
4. David C. Radley, Stan N. Finkelstein, and Randall S. Stafford, "Off-label Prescribing Among Office-Based Physicians," *Archives of Internal Medicine* 166, no. 9 (2006): 1021–26. *Available at* http://archinte.ama-assn.org/cgi/content/abstract/166/9/1021.

that off-label prescriptions for certain drugs were as high as 80%. Some physicians report that "almost all cancer chemotherapy is off-label."[5]

The prevalence of off-label prescribing can present a significant challenge to the government or *qui tam relator* because the FCA requires plaintiffs to prove that the alleged off-label promotion "caused" or "induced" the provider to prescribe the drug for an off-label indication.[6] While every investigation is unique, there are two significant overarching themes that often factor into the proof of causation and damages.

First, notwithstanding any alleged inappropriate marketing, healthcare providers exercise their own clinical judgment to determine which drugs to prescribe for their patients in connection with various on-label and off-label indications. Studies have found that healthcare providers prescribe drugs for off-label indications for a variety of reasons. One study, in particular, concluded:

> Off label use may originate from a presumed drug class effect, extension to milder forms of an approved indication, extension to related conditions…expansion to distinct conditions sharing a physiological link…or extension to conditions whose symptoms overlap with those of an approved indication.[7]

Second, some studies have concluded that marketing by pharmaceutical sales representatives has a relatively modest influence on healthcare providers compared to other sources of information. For example, a 2003 study concluded:

> Most importantly, PSRs [Pharmaceutical Sales Representatives] are not the only or even the primary source of information about drugs for physicians. Scientific papers, advice from colleagues, and a physician's own training and experience also influence prescribing practices. Indeed, most physicians view these other influences as far more important than that of PSRs. Peay and Peay (1990) report that out of fifteen potential information sources about drugs physicians rated PSRs twelfth in usefulness.[8]

---

5. Daniel B. Klein and Alexander Tabarrock, "Who Certified Off-Label?" *Regulation*, Summer 2004, 60–63.
6. Katherine A. Blair, "The FCA: Present Challenges and New Opportunities," *Health Lawyer* 23, no. 4 (2011), available from the American Bar Association.
7. Randall S. Stafford, "Regulating Off-Label Drug Use—Rethinking the Role of the FDA," *New England Journal of Medicine* 358 (2008): 1427–29.
8. Natalie Mizik and Robert Jacobson, *Are Physicians 'Easy Marks'?: Quantifying the Effects of Detailing and Sampling on New Prescriptions*, Institute for the Study of Business Markets, Report 9-2003, *available at* http://isbm.smeal.psu.edu/library /working-paper-articles/2003-working-papers/09-2003-are-physicians-easy-marks.pdf.

Thus, in light of the prevalence of off-label prescribing, providers' use of clinical judgment, and the factors other than pharmaceutical promotion to providers, proof of causation and damages in off-label marketing cases often requires careful analysis of providers' prescribing patterns. Below, we discuss empirical strategies to analyze providers' prescribing patterns in order to evaluate causation and damages in the context of off-label marketing allegations. We also note that the empirical strategies discussed below could be employed under a variety of FCA allegations and are not limited to allegations of off-label marketing.

Analytical framework for causation and damages

As is common in many legal contexts, our general framework for analyzing causation and damages is to compare observations from the actual world with benchmarks that represent a counterfactual "but-for" world in which the challenged conduct had not occurred.[9] In the context of off-label marketing allegations, that framework involves comparisons of instances where the alleged off-label marketing took place with instances where it did not. If all other relevant factors can be controlled for, the difference in providers' off-label prescribing patterns between these two regimes should provide a reliable measure of the effect of the alleged off-label marketing.

The specific nature of the alleged off-label marketing and the scope of the available data on prescribing frequently dictate the type of benchmark comparison that can be performed. If prescribing information is available only for providers who were subject to the challenged marketing, then the only feasible benchmark comparison may be across time for those providers. For example, if the alleged off-label marketing started at a certain point in time, then, all else equal, the subjected providers' prescribing patterns before and after that point could be compared to evaluate the effect of the off-label marketing. Such a comparison is commonly known as "before-and-after" analysis.

If post-marketing prescribing information is available both for providers that were subject to the challenged marketing and those that were not, then a feasible benchmark comparison may be across those groups. For example, if some providers were subject to off-label marketing while other providers were not, then, all else equal, differences between the two groups' prescribing patterns could be compared to evaluate the effect of the alleged off-label marketing. Such a comparison is commonly known as the "treatment-and-control-group" analysis.

Both the before-and-after analysis and the treatment-and-control-group analysis may have significant pitfalls, as we discuss below. However, if prescribing information is available both through time and across treatment and control groups, then "difference-in-differences" analysis can be used to better

9. *See, e.g., Bigelow v. RKO Radio Pictures, Inc.*, 327 U.S. 251 (1946).

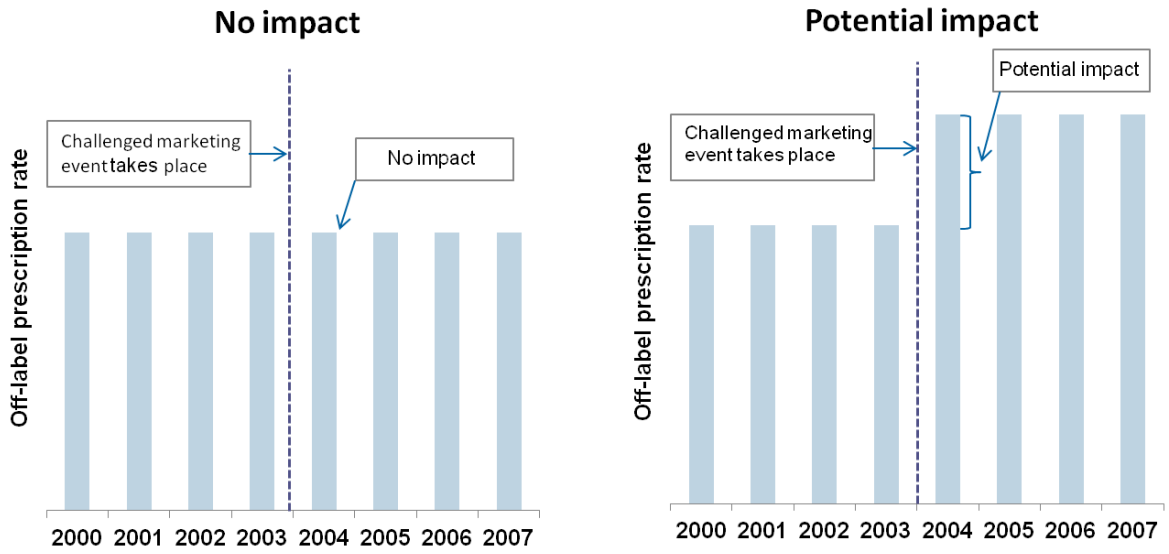
control for potentially confounding factors and, in theory, evaluate the effect of the alleged off-label marketing more reliably.

Before-and-after analysis

One way to determine the potential effect of off-label marketing on off-label prescribing is to evaluate how the pattern of off-label prescriptions changes after an alleged off-label marketing event occurs. Such events may include the implementation of a challenged marketing campaign or the date of a visit by a manufacturer's sales representative to a physician in which alleged off-label marketing occurred.

The analyst can evaluate whether and to what extent there is an increase in off-label prescribing at the time of the challenged marketing event, which can provide evidence concerning the effect of the challenged conduct and a basis for measuring damages. Figure 1 provides two contrasting hypothetical illustrations of before-and-after analysis. The illustration on the left shows that the off-label prescribing rate by the subject physician did not change after the challenged event, thus, all else equal, implying no impact. The illustration on the right shows that the off-label prescribing rate by the subject physician increased after the challenged event, thus, all else equal, implying potential impact.

Figure 1: Hypothetical illustrations of before-and-after analysis



There are several potential pitfalls to consider when conducting such before-and-after analysis. Suppose, for example, a provider's off-label prescribing increases following a marketing event, but only after a significant period of time has passed. In such circumstances, an analyst should

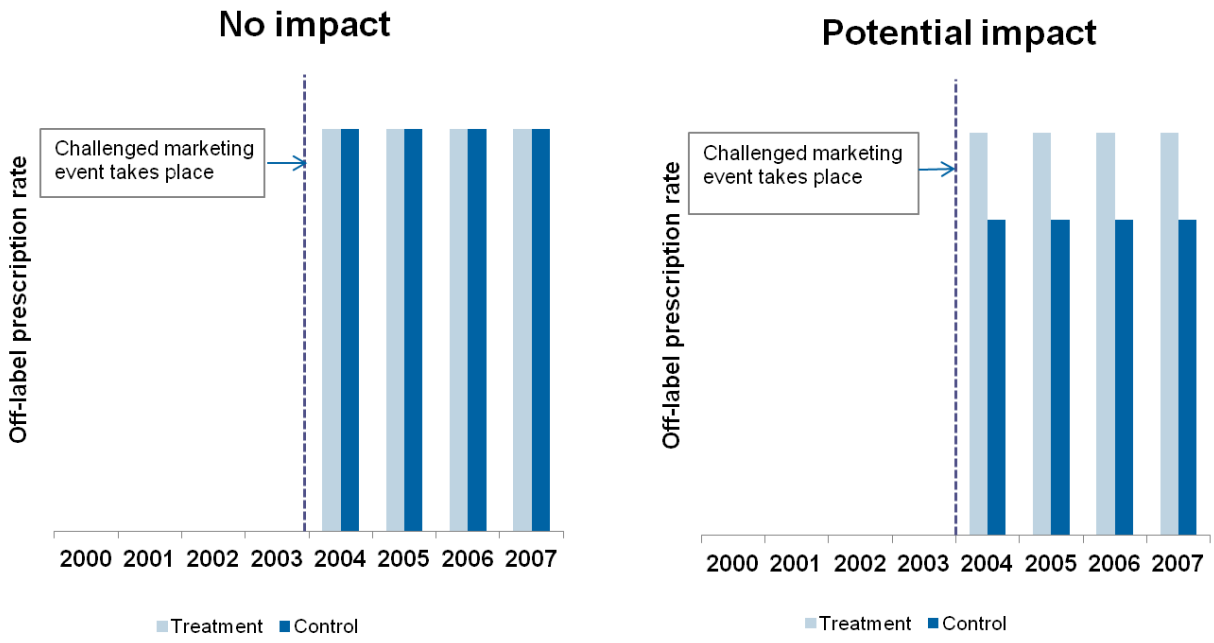
investigate whether other factors, such as the publication of relevant medical journal articles, better explain the increase in off-label prescribing. Another potential pitfall involves not carefully evaluating prescribing trends prior to the alleged marketing event. For example, the analyst may observe that a particular provider steadily increased their off-label prescribing prior to a challenged marketing event and continued that trend thereafter. Such a pattern suggests that the increase in off-label prescriptions merely reflects a pre-existing trend that may not be associated with the challenged conduct.

Stated more generally, the analyst must be careful not to confuse correlation with causation. That is, the fact that two events happen in conjunction with one another does not imply that one necessarily causes the other. Even when a causal inference appears likely at first glance, the analyst must be careful to rule out other potential explanations.

Treatment-and-control-group analysis

Another method for determining the potential effect of off-label marketing on off-label prescribing involves the comparison of the prescribing rates of providers alleged to have been targets of the off-label marketing (the "treatment" group) versus those who were not (the "control" group). In this framework, the analyst can measure whether the treatment group had a higher rate of off-label prescribing compared to the control group. In Figure 2, the illustration on the left shows that both the treatment and control group have similar rates of off-label prescribing after the challenged marketing event, thus, all else equal, suggesting no impact. In contrast, the illustration on the right shows a higher rate of off-label prescribing for the treatment group compared to the control group, thus, all else equal, suggesting a potential impact.

Figure 2: Hypothetical illustrations of treatment-and-control-group analysis

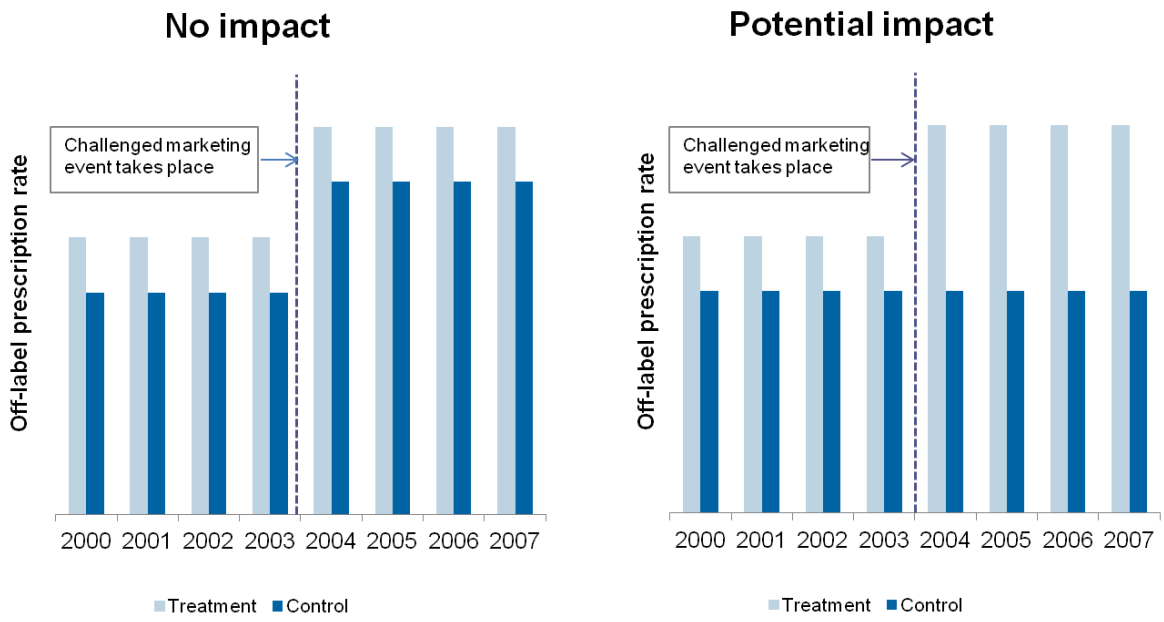


A critical consideration in the treatment-and-control-group analysis is whether the treatment and control groups are sufficiently comparable. For example, depending upon the specific allegations, it may be inappropriate to compare different types of providers or providers with different specialties. In any case, it is important for the analyst to carefully construct the control group to ensure that the analysis is not one of "apples and oranges."

Difference-in-differences analysis

When providers' prescribing data are available both through time and across treatment and control groups, a difference-in-differences analysis may provide the most reliable evaluation of the effect of alleged off-label marketing. Using difference-in-differences analysis, the analyst compares the change in the treatment group's off-label prescribing after an alleged off-label marketing event, with the change in the control group's off-label prescribing over the same time period. In Figure 3, the illustration on the left shows that the rate of off-label prescribing for the treatment group increased after the challenged marketing event. However, the control group also experienced a similar increase, which suggests no impact. In contrast, the illustration on the right shows that only the treatment group's off-label prescribing rate increased after the challenged event, suggesting a potential impact.

Figure 3: Hypothetical illustrations of difference-in-differences analysis



In essence, the difference-in-differences analysis combines the before-and-after analysis with the treatment-and-control group analysis and, in theory, addresses the major pitfalls of each approach. For example, the difference-in-differences method allows the analyst to control for both pre-existing trends and confounding factors, such as the publication of medical journal articles. However, the comparability of the treatment and control groups is still a critical factor that the analyst must address. Assuming comparability, if the treatment group's off-label prescribing increases more than the control group's off-label prescribing, then, all else equal, this may be reliable evidence of causation.

Econometric analyses

While each of the analyses discussed above can be performed as simple comparisons, they can also be performed using econometric techniques that attempt to control for a variety of other confounding factors and, in theory, provide more robust results. However, discussion of the relevant econometric techniques is beyond the scope of this brief summary.