Intern. J. of Research in Marketing 31 (2014) 65–77

Contents lists available at ScienceDirect

Intern. J. of Research in Marketing

journal homepage: www.elsevier.com/locate/ijresmar

The commercial contribution of clinical studies for pharmaceutical drugs

Ashish Sood [a,*], Eelco Kappe [b,1], Stefan Stremersch [c,d,2]

[a] Wharton School of Business, University of Pennsylvania, United States
[b] Smeal College of Business, Pennsylvania State University, University Park, PA 16802, United States
[c] Erasmus School of Economics, Erasmus University Rotterdam, Burgemeester Oudlaan 50, P.O. Box 1738, 3000 DR Rotterdam, The Netherlands
[d] IESE Business School, Universidad de Navarra, Spain

ARTICLE INFO

Article history:
First received in 25 October 2011 and was under review for 7 months
Available online 6 October 2013

Area Editor: Eitan Muller
Guest Editor: Marnik G. Dekimpe

Keywords:
Pharmaceutical marketing
DTP (direct-to-physician promotion)
DTCA (direct-to-consumer-advertising)
Reviews
Clinical studies
Time series model

ABSTRACT

Pharmaceutical drugs are rigorously evaluated through clinical studies. The commercial consequences of such clinical studies, both to the promotion for and sales of drugs, are largely under-researched. The present study answers the following research questions: 1) How does the evolution of clinical study outcomes affect product sales? 2) How does the evolution of clinical study outcomes affect a firm's promotion expenditures to physicians and consumers? 3) Is the assessment of the responsiveness of sales to promotion expenditures biased when the analyst omits the role of clinical studies? We summarize a comprehensive body of clinical studies in three metrics: valence, dispersion, and volume. We extend the literature with the following findings. A higher valence and volume of clinical studies (i.e., more positive and larger number of studies) increase sales. A higher valence of clinical studies increases spending on both direct-to-consumer advertising and direct-to-physician promotion. A higher dispersion among clinical studies decreases spending on direct-to-consumer advertising. A higher volume of clinical studies has no effect on direct-to-physician promotion, but decreases direct-to-consumer advertising. Furthermore, the results show that omitting these metrics from a market response model leads to an overestimation of the responsiveness of sales to promotion expenditures.

1. Introduction

Pharmaceutical firms or independent researchers conduct clinical studies to test and compare the efficacy of drugs with therapeutic alternatives or placebos. They use standardized protocols under controlled conditions to generate scientifically valid results. Firms, researchers, or journal publishers, among others, often translate clinical studies published in scientific journals in press releases that are picked up by mass media (Polidoro & Theeke, 2012). Thereby the outcome of clinical studies may affect sales of and promotion for the respective drug. The most common promotion efforts in the pharmaceutical industry are direct-to-physician promotion (DTP), such as detailing and journal advertising, and direct-to-consumer advertising (DTCA) (Stremersch, 2008; Stremersch & Van Dyck, 2009).

Consider, for example, the publication of three clinical studies on Lipitor in the last quarter of 2002 (Athyros et al., 2002; Colivicchi et al., 2002; Olsson et al., 2002). All three clinical studies reported a lower drug efficacy of Lipitor than earlier studies over three different patient populations. In that quarter, the sales of Lipitor grew only 2%, compared to a median growth of 3.5% of prior periods. Pfizer also substantially decreased its promotion efforts towards both physicians and consumers to its lowest level in four years. To uncover what relationships of such type exist in a large sample, we address the following questions:

- How does the evolution of clinical study outcomes affect the sales of a drug?
- How does the evolution of clinical study outcomes affect a firm's promotion expenditures to physicians and consumers for that drug?
- Is an assessment of the responsiveness of sales to promotion expenditures biased when the analyst omits the role of clinical studies?

We collected a comprehensive body of clinical studies on statins, published both prior to and after approval. The sample also includes published meta-analyses of clinical trials. Inspired by the marketing literature on user and expert reviews, we characterize the evolution of clinical studies using three time-varying metrics: valence, dispersion, and volume (Basuroy, Chatterjee, & Ravid, 2003; Chevalier & Mayzlin, 2006; Chintagunta, Gopinath, & Venkataraman, 2010; Godes & Mayzlin, 2004; Liu, 2006; Onishi & Manchanda, 2012; Sun, 2012). We define valence of clinical studies as the average efficacy of a drug to achieve a pre-determined outcome across a sample of studies. For example, we measure the valence of clinical studies of a statin at a certain point in time as the average reduction in low-density lipoprotein (LDL) cholesterol reported across all clinical studies available at that time. Dispersion of clinical studies at a certain point in time is the variance in this efficacy reported across all clinical studies available at that time. Volume of clinical

* Corresponding author. Tel.: +1 678 205 9931. Professor of Marketing, Georgia State of University, Atlanta.
E-mail addresses: a1sood@gmail.com (A. Sood), erk11@psu.edu (E. Kappe), stremersch@ese.eur.nl (S. Stremersch).
[1] Tel.: +1 814 867 0226.
[2] Tel.: +31 10 408 87 19; fax: +31 10 408 9160.

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http://dx.doi.org/10.1016/j.ijresmar.2013.07.007

studies at a certain point in time is the total number of clinical studies that report a drug's efficacy up to that point in time.

The application of these three concepts to clinical reviews (i.e., clinical studies are "reviews" of a treatment by trained scientists) is new and we show below that this new conceptualization leads to relevant insights. Currently, the predominant approach in pharmaceutical research to account for conflicting evidence from multiple studies is to meta-analyze such studies (Whitehead, 2002), which include summarizing the body of clinical studies on a drug by valence, and to a certain extent, dispersion. Prior studies have also examined the number of studies (i.e., volume of studies) (Adams & Griliches, 1996).[3] However, none studies the joint evolution of valence, dispersion, and volume of clinical studies and their effects on promotion expenditures and sales.

In this paper, we develop hypotheses on the effects of valence, dispersion, and volume on direct-to-consumer advertising, direct-to-physician promotion, and sales. We model the dynamic impact of these variables on one another through a random coefficients vector error correction model that controls for the heterogeneity across drugs and the endogeneity of promotion expenditures. Depending on the outcomes of unit root tests, we use the long-term or cumulative effects to test our hypotheses.

We extend the sparse literature in this domain in several ways. First, we use a richer conceptualization of clinical studies, i.e., the exact outcome measure of each clinical study. While Azoulay (2002) and Chintagunta, Jiang, and Jin (2009) code studies as negative, neutral or positive, we operationalize valence as a continuous measure. Also, we add dispersion and volume, thereby offering a more complete conceptualization. Second, Azoulay (2002) studies H_2-antagonists from 1977 to 1993. This means his sample predates DTCA, while ours does not, as it runs from the category's inception in 1982 till 2007. Therefore, Azoulay (2002) studies only detailing and journal advertising, not DTCA. Since 1997, DTCA has become an important component of pharmaceutical firms' promotion strategy, especially in the statin category. The contrast between firms responding through detailing to physicians or advertising to consumers is conceptually interesting. Third, Azoulay (2002) estimates a static demand model with homogeneous effects across brands. We develop a dynamic model, which is, as also conceded by Azoulay (2002), a more appropriate modeling framework, and we allow for heterogeneous effects across brands. Fourth, we assess whether the omission of clinical study outcomes in sales response models biases the promotion estimates, which has not been done before.

We derive the following new findings that extend the literature cited above. A higher valence of clinical studies increases direct-to-consumer advertising, direct-to-physician promotion, and sales. A higher dispersion of clinical studies decreases spending on direct-to-consumer advertising, but does not affect direct-to-physician promotion or sales. A higher volume of clinical studies has no effect on direct-to-physician promotion, but decreases direct-to-consumer advertising. A higher volume of clinical studies also increases sales. Taken together, these results suggest that while firms rush to inform physicians and consumers of improved clinical evidence, they reduce advertising to consumers when the results disconfirm prior findings (higher dispersion) or when many studies are released (higher volume). Furthermore, we find that omitting clinical study outcomes from a market response model leads to an overestimation of the responsiveness of sales to promotion expenditures.

These results hold several relevant insights for managers and researchers. First, our method is able to quantify the commercial value of clinical studies. We show how the total effect of a clinical study on sales is composed of the direct effect on sales, ceteris paribus, and an indirect effect on decisions on promotion expenditures, which subsequently may affect sales as well. Second, our results provide insights into pharmaceutical firms' reaction to clinical study outcomes. Firms can use this information to anticipate competitors' actions. Third, for analysts measuring the impact of pharmaceutical promotion on sales, we show that one needs to account for clinical studies in the econometric model.

[3] While this measure is sometimes weighted by citations, we choose not to do that as citations are noisy measures of knowledge flows (Roach & Cohen, 2013). Instead we measure the volume by only selecting clinical studies from the top quartile of journals.

2. Theory

This section provides the theoretical background on clinical studies and pharmaceutical firms' promotion to patients and physicians. We then develop hypotheses on how clinical studies may affect both firms' promotion expenditures and drug sales.

2.1. Background: clinical studies and drug promotion to patients and physicians

Trained scientists conduct clinical studies through systematic observation, measurement of, and experimentation with a drug using the scientific method. They adhere to strict protocols of regulators and institutes. Scientists from drug manufacturers, their competitors, or independent research institutes (e.g., universities) may conduct clinical studies. We use clinical studies to refer only to testing on humans.

One typically discerns clinical studies across four phases. Phase 1 testing is typically conducted on healthy volunteers to monitor safety and side effects. Phase 2 and Phase 3 testing is typically conducted on patients suffering from the disease that the drug targets. After approval and launch, Phase 4 clinical studies test the drug on even larger numbers of patients or on specialized groups of patients.

Independent clinical studies are more common post-launch than pre-launch. When a drug manufacturer sponsors researchers, the latter are required to reveal this sponsorship. Regulatory bodies or scientific journals publish guidelines for the reporting of clinical studies, such as on drug safety, side effects, and efficacy.

The sponsorship of clinical studies (see for more details DeAngelis & Fontanarosa, 2008), their diversity in design, and patient population may drive dispersion in study outcomes. Sponsorship bias – manufacturers often report a higher efficacy of their drug than competitors or independent researchers – may have multiple causes. First, selection bias may exist in project selection (e.g., by choosing a weaker competitor or a more favorable testing condition) (Doucet & Sismondo, 2008). Manufacturers may also stop a clinical study before completion if the initial results are unfavorable (Lexchin, Bero, Djulbegovic, & Clark, 2003). Both strategies may inflate the valence of the body of clinical studies. Another important goal of manufacturer-sponsored studies is to establish a consistent profile of the drug across studies (Sismondo, 2009). Independent researchers or competitors may have an incentive to balance positive claims by testing the drug in less favorable conditions, affecting valence, dispersion, and volume.

Firms may respond to clinical study outcomes through direct-to-consumer advertising or direct-to-physician promotion, the two most important types of marketing spending among branded pharmaceutical firms. Direct-to-consumer advertising may increase drug awareness, simplify complex information on the drug to facilitate comprehension, encourage patients to discuss new treatment options with their physicians, or increase compliance as a result of better education and involvement. While direct-to-consumer advertising positively influences stock returns (Osinga, Leeflang, Srinivasan, & Wieringa, 2011), most research finds direct-to-consumer advertising to have only a weak effect on category sales (Iizuka, 2004). Research on brand sales concludes that direct-to-consumer advertising may moderately increase physician visits (Liu & Gupta, 2011), while it has an even more limited effect on brand choice, if it has any effect at all (Iizuka & Jin, 2007; Stremersch, Landsman, & Venkataraman, 2013).

Direct-to-physician promotion typically has a positive impact on prescriptions (Manchanda & Honka, 2005), though some studies have reported these effects to be modest (Mizik & Jacobson, 2004).