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Ghost-Managing and Gaming Pharmaceutical Knowledge

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In his chapter in this volume (chapter 1), and echoed in a number of the other chapters here, Alex Csiszar describes how gaming metrics of science productivity was an immediate, possible consequence of the use of metrics—recognized in Goodhart's law—and an immediate concern in early discussions of metrics derived from the Science Citation Index. Gaming the system occurs when moves that are not against the rules, or that can be made to appear to be not against the rules, lead to some kind of surplus value. The truth of Goodhart's law, then, is a consequence of a more general kind of opportunism that fills "economic" (in a broad sense) niches. Particular instances of gaming can reveal both some possible opportunistic actions and the economic structures that make them possible. In this chapter, I focus more on the former, but try not to lose sight of the latter.

Here I describe an arena where related economies meet, and where various goods can be created by moving resources from one into another. The economies in question are those of medical science, medical practice, and pharmaceutical marketing. One of the results of the meeting is the publication of medical journal articles that look like reports of academic science, but that have been largely or wholly created by many corporate actors working together, with the ultimate goal of influencing prescriptions. Pharmaceutical companies and their agents control or shape, in ways that are not entirely visible, multiple steps in the research, analysis, writing, publication, and dissemination of significant amounts of medical science. I call this the "ghost management" of medical science.

Most of the clinical trial research that the pharmaceutical industry funds is handled by contract research organizations (CROs), companies that can run all different aspects of clinical trials. The data that CROs produce is typically analyzed by pharmaceutical company statisticians, reported in articles written by medical writers, and guided through to publication by dedicated publication planners. Publication plans parcel

data and other information for journals in ways that will be recognized and respected by various important physician and researcher audiences. Typically, it is only after the articles are drafted that authors are recruited. Authors are generally seen as "key opinion leaders" or "KOLs": doctors and researchers valued for their status within—or at least participation in—their specialties, and with whom the companies have established relations. In addition to having credibility, authors may be chosen because they already agree with the conclusions of the articles, or because they are prospective speakers on the drugs at issue. The articles form the basis of company-funded presentations by KOLs at conferences, in continuing medical education courses, and in innumerable small-scale events in clinics and restaurants, as part of what are known as "speaker programs." Company sales representatives and medical science liaisons—the latter are staff who interact with physicians and researchers primarily about the science that supports products—also distribute articles in visits to and exchanges with physicians.

Even in the sketch in the previous paragraph, we can see the pharmaceutical industry leveraging academic value by gaming academic communication. Pharmaceutical companies have joined the communication structures of academic science, making contributions that look as much as possible like good academic science, but that help to support commercial aims, in the form of encouragement to physicians to prescribe. In their speaker programs and door-to-door delivery of information, the companies have added new forms of communication, built on top of traditional academic forms. The medical science that pharmaceutical companies produce and circulate leads to drug prescriptions. In the following, I add some details to the picture I have just presented, displaying different forms of the leveraging of academic value, including one that takes us into the realm of metrics.

My research here draws on a wide variety of kinds of communications internal to the industry. In particular, it is largely based on my and two research associates' attendance at a number of industry conferences between 2007 and 2017, where people who are insiders make presentations on issues of publication planning, KOL management, or speaker programs (for more details see Sismondo and Chloubova, 2016; Sismondo, 2018). Much of my work focuses on what Finn Brunton (this volume, chapter 18) calls "secondary markets" around pharmaceutical research and marketing. For the sake of prudence and in accordance with my research protocol, I anonymize all sources, even though some of them were speaking in essentially public venues.

Publication Planning

The construction of industry-sponsored articles almost always involves publication planners. According to planners, their work can and should start even before the research does, contributing to research design, mapping out key messages, and designating different articles for different audiences and journals. Once the research is available, publication planners hire medical writers, contact potential authors, negotiate with various interests and departments within the pharmaceutical companies, and shepherd the articles through journals' submission and revision procedures (Auti et al., 2016). Ms. I, a planner working within a pharmaceutical company, says:

> This is what utopia looks like from an industry perspective. We have agreement and alignment on a plan, not even just a publication, a full plan, investigators on board, agencies lined up, everybody ready to play and we're going to get this done in a timely way, in an orderly fashion, and things work like clockwork.

The best publication plans comprehensively address research, development, presentations, and publications; appendices give the relevant data for each of the meetings and journals to which abstracts and papers will be submitted—the audiences they reach, their impact factors, their rejection rates, and publication lead times (Complete Healthcare Communication, 2006). A plan may also describe other communication opportunities, such as symposia and roundtables, journal supplements, advisory board meetings, monographs, slide programs, formulary kits, and more. Planners have been known even to create entirely new journals for particular projects, though that seems to be a rare and scandalous occurrence (Grant, 2009).

At the same time, planners should be responsive to changing circumstances and to the changing priorities of the company. Thus they might need to arrange for the production of a letter to the editor in response to an unfavorable study or the needs of a public relations campaign. Mr. D, a planner working for a large pharmaceutical company, illustrates this when he talks about supporting his company's key messages:

> At the beginning of the year, we kind of have a scientific strategy for every product, saying, y'know, these are the key messages that we're hoping to get out, depending on what clinical data we have available. We'll look at all the points that the upper management folks would like us to try and see if we have the data to address, and then we'll go through it point by point and try to see.

The biggest growth of publication planning occurred in the 1990s and probably was connected to other changes in the global pharmaceutical economy. That decade saw an enormous increase in global sales of pharmaceuticals, at an average rate of over ten percent per year (World Health Organization, 2004). This surge was spurred by an increasing number of blockbuster drugs and consistent high sales growth in the United States. There was also a change in the structure of research: in 1990, seventy percent of pharmaceutical industry research funding went to universities and teaching hospitals, whereas in 2000, seventy percent went to CROs (Mirowski and Van Horn, 2005), a level that now seems stable (Westrock, 2016). The simultaneous rise of the publication planning and CRO industries almost certainly is not coincidental, since CRO research can be planned and harnessed to marketing goals more easily than can academic research: CROs, unlike academics, have little interest in publishing the results of their studies.

Planners recognize that their work has marketing value, and publication planning agencies often advertise their work in terms of the contribution it can make to marketing. Tongue in cheek, industry consultant Ms. S asks the audience at one meeting, "By the way, is anything you do ever used in a promotional context? Oh yeah!" The promotion can be very broad. A publication plan accompanying the launch of a likely blockbuster drug can include more than fifty articles published over three or so years (Healy and Cattell, 2003; Ross et al., 2008). A chart presented at an industry seminar entitled "Publication Planning 101," showing the number and type of publications per year for a fictional new product, displays roughly ninety articles to be published over the course of five years. These are labeled: clinical efficacy, clinical pharmacology, review, case report, letter to the editor, and quality of life. In another context, Ms. S says, "The newest thing right now is disease states. … You all know what I'm talking about, where you don't mention the name of the drug but you talk about the disease."

Pharmaceutical companies typically arrange for KOLs to serve as all or the majority of authors on manuscripts. By using KOLs as authors, publication planners can give articles a veneer of having been written by independent researchers, instead of by a coordinated industry team. A KOL author thus increases the perceived credibility of an article and also hides features of the research process and analysis. Because of pressure from journal editors, the work of medical writers is increasingly being recognized in the acknowledgments sections of articles, but company statisticians and researchers, reviewers from an array of departments, and publication planners are rarely mentioned.

In general, KOL authors are very unlikely to have worked closely with the data they are reporting. Pharmaceutical companies initiate and fund the planning, research, analysis, writing, and placing of articles, and typically maintain control of data throughout. Industry representative Dr. Q even argues that authors should not be given *access* to the data, because they may lack skill, and they may have their own agendas: "As the owners of the study database, the sponsors will decide who will have access to the database.... PhRMA [Pharmaceutical Research and Manufacturers of America, the US industry lobby group] companies commit to making a summary of the results available to the investigators." According to Mr. B, working for an independent planning agency, fifty percent of companies show only the penultimate draft to authors, to solicit their input. As a result, ghost-managed articles almost always violate naïve readers' expectations about their trajectories, and generally violate journals' authorship criteria—though publication planners try to make it possible to make a case that their authors technically meet those criteria.

The KOLs may have multiple reasons for agreeing to serve as authors on these manuscripts. They add articles to their CVs, and, as I discuss below, these articles are likely to be amply cited. Although pharmaceutical companies do not pay for authorship, they may ask authors to give presentations of, or related to, the research, for which the authors are generously paid. Finally, it can be flattering to be targeted as an expert, and the manuscripts themselves may even contain more flattery, as this short excerpt from a legal deposition of a publication planner, discussing a ghost-managed review article, shows:

Q. All right. So before Dr. M. Brincat [the eventual author] saw the outline, Designwrite [the publication planning firm involved] had done the medical research, the literature research, to determine whether there was sufficient scientific evidence to support a scientific platform for this article. An outline was drafted and then Mr.... approached Brincat and Brincat agreed to be an author; is that correct?

A. That is correct, because it mostly cited Dr. Brincat's research. (US District Court, 2006)

Editors of all of the important medical journals are aware of the process, and almost every publication planning conference includes a panel of editors. While the editors typically condemn ghostwriting, they seem to accept that the strong pharmaceutical industry presence in medical research necessitates the ghost management of research and publication. These editors and their journals also value the articles, which, again, tend

to be respected and amply cited, and which may turn into immediate revenue if the companies sponsoring them want to buy reprints for distribution. It is striking that, despite the occasional exposé revealing ghost-written articles, retractions because of industry ghosting are extremely rare or nonexistent (Jones, 2009).

Speaker Programs and Other KOL Activities

For fifty years or more, sales representatives, medical science liaisons, and, recently, independent firms have been identifying potential KOLs, establishing relations with them and developing them into more effective speakers and advocates for companies: "A key task of a pharmaceutical rep's job is to help transform influential doctors into speakers and consultants who know the rules of the game and are quite adept at negotiating a stipend and 'working the crowd'" (Oldani, 2004; see also Sismondo, 2018).

The industry recognizes different kinds of KOLs, requiring different forms of interaction. Ordinary physicians—either general practitioners or specialists—are paid to speak to other physicians as members of speaker bureaus for particular drugs: they might address other physicians at lunchtime talks organized by sales reps, or serve as after-dinner speakers at physicians' events, also organized by sales reps. Medical researchers' value to pharmaceutical companies might stem from any number of activities: they might be paid to speak to researchers or patient groups or at continuing medical education sessions; they might be consulted on any number of medical, marketing, or research issues; they might serve as authors of ghost-managed medical journal articles; or they might contribute to research either by recruiting patients for trials or by initiating their own trials.

Like publication plans, speaker programs can be large. Pharmaceutical company manager Mr. E, presenting at a KOL management conference, raises the specter of an investigation of a speaker program: "When you say 'I need seven hundred to one thousand speakers in this activity,' the questions [that are] going to get pushed back to you in investigations are, 'Why do you need so many? How many is each speaker going to do? Why did you need a thousand?'" Mr. E's concern is that investigators will conclude that some speakers are being trained and paid not because they are effective communicators but because they are important prescribers. There is a continuum from KOLs employed primarily to change other physicians' prescribing patterns to those employed primarily to change their own prescribing patterns (which is generally illegal). The

latter suggests a devious way of leveraging academic-like communication structures, influencing people by hiring them to speak.

With physician KOLs, the goals and consequent relationships are straightforward, since the physicians are simply hired to give talks and typically are given zero latitude in their delivery. Researcher KOLs, though, are treated so that they feel more like partners in medical science and education. Interactions with them need to be subtle, especially since much of KOLs' value to the companies stems from their independence from those companies, creating a real tension. Still, the needed independence does not stop KOL management experts from repeatedly indicating that KOLs can be used as important mediators for pharmaceutical companies. Here is Ms. C speaking to an audience of KOL managers and others:

> [A] KOL point person can help you and the organization make sure that you are … identifying the right expert for the right need and able to work with them at the right place and time and be able to deliver a KOL plan that's aligned to their scientific objectives. … Particularly as you start to enter Phase One, Phase Two [trials], and, you know, these molecules are moving along, it looks to have some promise—okay there are unique aspects perhaps about the mechanism of action—it's going to be very important to help start to educate the community, the physician community, the patient community, the professional societies on this mechanism of action [and] on the disease state itself.

Researcher KOLs can smooth the path to acceptance of drugs and diseases by helping to shape the background of accepted issues and opinions in a field. They might participate in industry-sponsored workshops and author key papers, thereby becoming the experts to whom the FDA could turn for advice on drug submissions and to whom the media could turn for interviews and information. In this way, they act as mediators between pharmaceutical companies, the FDA, physicians, and potential consumers (Fishman, 2004).

A Citation Puzzle

The ghost management of medical research presents a citation puzzle linked to companies' gaming of academic communication systems. Gorry (2015) analyzes a group of ninety-two articles known to be ghost-managed, identified in documents from three legal proceedings. Among other things, Gorry notes that ghost-managed articles were cited approximately ten times more often than were typical other articles in the same journals—and almost none of the difference is explained by a difference in prestige of the authors (personal communication). Healy and Cattell

(2003) had earlier analyzed a subset of that group, and, unsurprisingly, the two studies come to some overlapping conclusions. Healy and Cattell compare their group of fifty-five ghost-managed articles on a particular drug with other articles on the same drug published in the same period: ghost-managed articles were cited between 2.4 and 2.9 times more frequently than matched counterparts.

I suggest three possible explanations of the high citation rate of ghost-managed articles, all of which are very likely right, though I can only point to factors that make each one plausible.

First, ghost-managed articles may be more *cite-worthy* than their various counterparts. Pharmaceutical companies sponsor the majority of medium-sized and large clinical trials, the kind of study that is most valued in the medical world. The resources of pharmaceutical companies enable them not only to run solid trials, but also to produce articles that have all the hallmarks of good science. If ghost-managed articles are "counterfeits" and independent ones are "authentic," in this case the counterfeit appears to be as high quality as is the authentic.

Second, ghost-managed articles may be more cited because they have better distribution than their counterparts. As marketing vehicles, these ghost-managed articles need to be read, or at least seen. Pharmaceutical companies have excellent distribution systems for their articles and for the information contained in them. The companies pay for presentations by KOLs at conferences, continuing medical education courses, clinics, and after-dinner events. Sales representatives and medical science liaisons provide reprints of articles to physicians, including academic physicians. Occasionally, companies engage in mass mailings of reprints. Ghost-managed articles, then, are tremendously better circulated than are independent articles.

Third, the ghost management process likely leads to an interesting version of self-citation. A publication plan that involves fifty or a hundred articles provides many potential entries in a reference list. Later articles can cite earlier ones, and all can cite articles from earlier publication plans, and not just earlier articles by particular authors. Describing an episode in her work as a medical writer, Larkin (1999) writes:

> I agreed to do two reviews for a supplement to appear under the names of respected "authors." I was given an outline, references, and a list of drug company-approved phrases. I was asked to sign an agreement stating that I would not disclose anything about the project. I was pressured to rework my drafts to position the product more favorably.

Presumably, the list of references she was given was just as drug company-approved as was the list of phrases—medical writers and publication planners describe the literature review as a key step in the development of an article. Indeed, it would be curious if reference lists were *not* skewed toward the company's previous articles, because those articles would tend to support the company's commercial interests and because those would be the articles or references to hand. If such self-citation exists, it is unusually invisible, in that the self-references are not to an individual, a laboratory, or a department, but rather to a set of publication plans and a company.

Conclusion: Multiple Leverage Points

Pharmaceutical companies have joined academic medicine's research and communication structures. They participate both covertly and overtly, sometimes choosing to build medical knowledge minimally marked by conflicts of interest, and sometimes choosing to establish strong connections between scientific evidence and brands.

Not only do companies participate, they participate with more and better resources than are available to independent academics. Their ability to hire CROs allows them to run randomized, controlled trials worldwide, on drugs for varied conditions; clinical trials produce the kind of knowledge that is most valued within medicine. Companies produce articles for academic journals that look like independently produced articles and have independent academics as authors, but that are likely to be more influential than are independently produced articles.

Not only do companies participate, they innovate. Building on forms like academic conferences and continuing medical education, they have developed sponsored research workshops and speaker programs, at which their KOLs give presentations that have the look and feel of presentations in academic research and education contexts, and sometimes might even be confused for independent work. Along the way, the companies may be using these forms to convince the KOLs themselves to prescribe their products.

The intersection of different economies means that various different goals and metrics are at play here. A ghost-managed article contributes to medical knowledge. For pharmaceutical companies, the content of articles is important, because it can serve as a justification for prescriptions of their products. For those companies, at issue is the monetary return on

investment of the publication of research. Although this can be difficult to measure, there are attempts to measure the increased prescriptions resulting from particular articles. For a KOL author, an article represents another line on a CV and a contribution to prestige; it also may lead to industry-paid speaking engagements and to new citations. For a journal, a ghost-managed article contributes to its positive reputation for publishing clinical and other research; the article is also likely to contribute to its impact factor, and if the sponsoring company uses reprints of it for promotion, the article could provide cash revenue.

Consistent with the insights of Marie-Andrée Jacob in this volume (chapter 19), ghost-managed articles are not simple counterfeits or fakes, standing in opposition to authentic or real articles. They are developed and constructed with considerable resources and skill, and rely on rich data. They are widely distributed and have real-world impact in the form of prescriptions. They are often exemplary pieces of medical science—albeit medical science created for marketing purposes, and with commercial interests driving the work. Moreover, these articles rely for their effectiveness on at least a limited amount of collaboration with academic medical science—in the form of offering authorship of articles, with the endorsement that that implies. While, because authors typically do not meet journals' authorship criteria, there is typically misconduct, there is a sense in which the misconduct needs to be carefully teased apart from more prototypical misconduct, such as faking data. Instead, pharmaceutical companies are now the biggest contributors to the evidence base of medicine, ghost-managing apparently high-quality, interest-driven scientific knowledge: gaming academic communication and leveraging academic value for commercial goals.

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