

## Pharmaceutical Companies and Ophthalmic Research

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Industry funding for medical research is essential to advance the treatment and prevention of many diseases. Still, dangers exist when researchers collaborate with industry. Commercial interests have an increasing impact on what appears on the pages of medical journals, a finding criticized by the mainstream media and in the *New England Journal of Medicine*,<sup>2-4</sup> among other venues. This editorial discusses some of the issues that editors must consider in selecting new information for the readership.

Before 1980, medical research was performed primarily in academic medical centers without much influence from commercial companies. An amendment to United States patent law called the Bayh–Dole Act, passed in 1980, permits universities to commercialize products and inventions without losing federal funding. Bayh–Dole succeeded in stimulating advanced technological invention and sped its transfer from university laboratories into private industry. In 1984, private companies contributed about \$26 million to university research budgets; by 2000, they were contributing \$2.3 billion and providing funds to universities at a time when practice income was decreasing while operating costs were increasing. Of the \$6 billion in industry-generated money for clinical trials worldwide each year, about \$3.3 billion goes to investigators in the U.S.<sup>5</sup>

In the early 1980s, academic institutions partnered with pharmaceutical companies to develop research centers in which students and faculty members essentially carried out industry research.<sup>2,3</sup> Academic medical centers provided the design and patients for trials, whereas companies enjoyed the prestige of working with academic researchers and benefited from the academic publications that helped to market their products. Plus, the institutions could patent and license new products developed by faculty members and share royalties with the researchers.

Although academic medical institutions enjoyed a period of little competition and a tremendous influx of research dollars, pharmaceutical firms became frustrated by prolonged administrative difficulties with institutional review boards and academic research offices.<sup>3</sup> Clinical trials seemed to proceed slowly at academic medical centers,

largely because academic physicians have competing responsibilities in teaching, research, and patient care as well as dealing with the academic administrative complexities of clinical trials. Pharmaceutical companies lost time and money in the highly competitive global race for new drugs and devices.

Networks of commercial contract-research organizations (CROs) and site management organizations (SMOs) rose in a direct response to the slow academic responses and desire to expedite clinical trials.<sup>3</sup> In 1991, 80% of industry money for clinical trials went to academic medical centers; by 1998, the figure had dropped to 40%.<sup>3,6</sup> Evidence suggests that the commercial sector completes trials more rapidly and more cheaply than academic medical centers.<sup>7</sup> Industry now employs top-level research physicians to design and interpret drug trials, and community physicians have become a reliable source of patients. Several hundred CROs now compete in the drug trial business, employing physician–scientists, pharmacists, biostatisticians, and managers.<sup>3</sup> Drug companies can create their own study designs but contract with CROs to develop a network of sites, implement the trial protocols, and send report forms to the drug company, which performs its own data analysis. Contract-research organizations may also subcontract with for-profit SMOs that organize networks of community physicians, encourage and assist in enrollment of patients, and deliver the clinical trial data or forms to the CRO. Site management organizations provide community-physician investigators with administrative support and help market investigators' services to pharmaceutical companies.<sup>3,8</sup> They have been criticized for producing data of poor quality, inadequately training investigators, and costing more than a system of independent sites unassociated with an SMO.<sup>3,8,9</sup> The end result is that some trials may have 4 layers of involvement (pharmaceutical company, CRO, SMO, and physician investigator) and there is intense competition for drug-trial money among the hundreds of CROs, SMOs, academic medical centers, and independent nonacademic sites.<sup>3</sup>

Several academic medical centers are now fighting the trend toward commercialized drug trials by creating research networks.<sup>3,6,10</sup> With funding from both industry and National Institutes of Health sources, these networks include academic researchers and community-based physicians. These networks can institute procedures for training investigators; establishing centralized contracting, budgeting, and reimbursement systems; and preparing and monitoring institutional review board approval. Pharmaceutical company control is more likely when nonacademic investigators with limited expertise are hired.<sup>3</sup> Companies might tend to design studies favoring their products while not

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This editorial is part of a series on editorship by the editors of the three journals. The opinions expressed are solely those of the individual authors.

Drs Liesegang and Albert have no financial interests to disclose. Dr Schachat disclosed his when he became Editor.<sup>1</sup> During the past 2 years, his activities have not changed substantially. His employer, the Johns Hopkins University, receives research grants that support a fraction of his time from the National Institutes of Health, Alcon, QLT, Inc., and Novartis. During the past 2 years he has provided consulting services for Berlex, Santen, Concurrent Pharmaceuticals, Neovista, Eyetechnic, and Pfizer. These agreements were reviewed and approved by his employer.

sponsoring studies academic investigators believe are needed. Bero and Rennie discuss the methods companies might use to produce desired marketing results.<sup>11</sup> For instance, companies may study many surrogate end points but publish results only for those that favor their product.<sup>3,11,12</sup> Even if principal investigators have the capacity to analyze all the data from a large trial, companies might try to retain control over the data and analysis.

Pharmaceutical firms are primarily interested in new-drug applications to the Food and Drug Administration, whereas publication in prestigious journals is secondary. In industry-sponsored research, authorship may include the study designers, patient recruiters, and prestigious participants.<sup>3</sup> Some multicenter trials place publication responsibility with publication committees, which may be dominated by pharmaceutical or outside investigators. In other cases, the company or CRO might write the reports for publication, circulating draft manuscripts to the investigators, who will be listed as authors. Bodenheimer reveals a newer variation in which drug-trial reports are prepared by nonwriting authors and by nonauthor writers.<sup>3</sup> In this scenario, a professional medical writer develops the content of an article but is not named as an author; likewise, a clinical investigator who appears as an author has neither analyzed the data nor written the manuscript.<sup>13</sup> This pattern is more common in the commercial sector, where community-physician investigators may have little experience in writing or authorship.<sup>3,14,15</sup> In one study, 19% of the articles surveyed had named authors who did not contribute sufficiently to the articles to meet the criteria for authorship outlined by the International Committee of Medical Journal Editors.<sup>3</sup> Eleven percent had ghostwriters who contributed to the work but were not named as authors.<sup>16</sup>

Many academic medical centers insist on the investigator's right to publish the trial's results while allowing the company prepublication review.<sup>3</sup> Many researchers with industry funding experience delays in the publication of their study results,<sup>17</sup> while results of substantial numbers of clinical trials are never published at all.<sup>18</sup> Some contracts have forbidden disclosure of results for 3 years after the study without the company's consent,<sup>19,20</sup> and researchers have not been permitted to publish unfavorable results.<sup>20</sup> Other scenarios are detailed by Bodenheimer.<sup>3</sup>

Whereas some pharmaceutical research contributes to our basic understanding of disease, much is used to show advantages, often minimal, over competing drugs.<sup>3</sup> Perhaps our most promising researchers are merely supplying marketing information for the pharmaceutical companies rather than independently deciding what research is scientifically important.<sup>2</sup>

The majority of authors who responded to a survey believed their relationships with pharmaceutical companies had no influence on the recommendations they put forward in clinical practice guidelines: in contrast, almost 20% of the respondents believed their colleagues' relationships influenced the recommendations they put forward.<sup>21</sup> In considering a large range of reports of clinical trial outcomes, Chan et al reported that clinical trials are not only frequently incomplete in their data reporting, but also biased and inconsistent with their own protocols.<sup>22</sup> Published articles

and reviews that incorporate them may therefore be unreliable and overestimate the benefits of an intervention or drug therapy.

Although drug trials conducted through academic medical centers have a profit incentive, they have the potential to obtain a balance between the commercial interests of industry and the scientific goals of investigators. Trials conducted in the commercial sector with for-profit CROs and SMOs, however, are much more prone to an imbalance favoring industry.<sup>3</sup> Bodenheimer suggests the pharmaceutical industry reevaluate the risks inherent in its partnership with the commercial drug-trial sector and consider reestablishing research networks through academic scientists and institutions.<sup>3</sup> Other authors have made recommendations to resolve the problems of clinical drug trials, primarily focused on increasing the independence of investigators to conduct and publish their research.<sup>16,23-25</sup> Meanwhile, a working group of pharmaceutical representatives, clinicians, and editors has established and published a working document that encourages responsible reporting of clinical trials and would reduce inappropriate sponsor involvement.<sup>26</sup>

All editors are, or should be, concerned about the increasing commercial involvement in journal submissions. In many instances, there is lack of sufficient or significant end points in the protocols, lack of correlation with the original hypothesis of the study, evident dredging for significant statistics with insufficient importance, excessive commercial involvement in the writing or editing of the reports, and diffusion of the clinical trial result data so that the appropriate physicians may not have access to the overall drug or device profile. Commercial companies should follow the voluntary publication guidelines they are now developing and improve the development and management of clinical trials. Academia needs to streamline some of its bureaucratic practices to gain back these clinical trials and then provide more rigorous critique and reporting of data. Academic medical centers, moreover, need to be reminded of their mission and avoid being economically seduced. Editors and the public are scrutinizing these arrangements and submissions more closely and are poised to remind authors, sponsors, and institutions of the improprieties that are detected.

As editors of 3 major ophthalmic journals, we are faced with needed rejection rates of 70% to 80%. We are definitely paying attention to issues of authorship, sponsorship, involvement of third party CROs and SMOs, and other warning signals that may cast doubt on the independent and unbiased analysis of study data. Peer reviewers must insist on scientific and statistical rigor, requiring full disclosure of analyses attempted but not reported, roles of authors and nonauthors in manuscript preparation, and who has control of study data. In response to a review, authors and sponsors will be required to make changes to the manuscript to be more forthright, so that readers may judge for themselves the veracity of a scientific paper. Readers need to be alert to red flags as enumerated herein in the reports of clinical trials because reviewers and editors cannot always detect deficiencies in trial methodology and because some journals may not be as alert to these issues.

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