Restoring Confidence in the Pharmaceutical Industry

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ACK OF TRUST IN THE PHARMACEUTICAL INDUSTRY threatens the future of biomedical research. Although more than half of funded clinical trials in the United States are supported by industry and many scientists, clinicians, and others in industry are committed to advancing biomedical science and improving the health of patients, there is a need to restore confidence in pharmaceutical companies and the research they sponsor. As editors of a journal that publishes articles supported by industry, we are familiar with many of the complicated issues related to industry-supported and industry-analyzed studies. We have had discussions with leaders of the pharmaceutical industry about concerns they have regarding the erosion of trust in their companies. We also have had discussions with academic leaders and leading scientists about ways to improve the reputation of pharmaceutical industry research and have participated in initiatives to harmonize reporting by physicians, investigators, and others who have financial relationships with industry and other conflicts of interest.

The last 2 decades have seen major changes in the pharmaceutical industry. Consolidation among companies has occurred; revenues and profit margins have increased; and until recently, many “blockbuster” drugs had entered the marketplace. However, in more recent years, innovation leading to new product development has declined, resulting in limited numbers of new drugs and other agents in the once robust pharmaceutical pipeline. In 2013, the industry will face substantial drug patent expirations, with more than 40 brand-name products losing patent protection with an estimated value of $35 billion in annual sales. To maintain market share, some companies have proposed new uses for or minor modifications to existing products.

At the same time, the credibility of pharmaceutical company research has declined. Numerous high-profile reports involving some of the world’s largest and previously most well-respected companies have detailed serious concerns about manipulation and misrepresentation of data from industry-sponsored research. One report that compared information from efficacy trials included in US Food and Drug Administration (FDA) documents for approved new drug applications (NDAs) with information published in journal articles found that many clinical trials included in the NDAs were not published 5 years after drug approval had been granted. The study also found important discrepancies between the primary outcomes, statistical analyses, and conclusions reported in NDAs compared with that information reported in journal articles. The information found in published trials was often more favorable than the data reported in the NDAs. Moreover, some companies have incurred substantial fines for unethical and illegal marketing practices of approved products. In addition, a recent study suggested that clinicians devalue the credibility of industry-funded trials, as compared with the same trials characterized as having National Institutes of Health funding or having no source of support listed, and were less likely to prescribe a drug evaluated in a clinical trial that was supported by industry, even if the study was of high quality.

The pharmaceutical industry is confronted by other challenges. Society has become increasingly risk adverse, and patients are less tolerant of even rare adverse outcomes, which may not be detected even in large-scale randomized clinical trials designed as “efficacy studies,” with highly selective populations. But because virtually no drug is entirely safe, rare adverse events are inevitable, and some serious adverse events might not manifest until the drug is used in less carefully selected “effectiveness” patient populations that characterize clinical practice.

Should industry be held accountable for these adverse events? The health sector is viewed differently from other sectors of the economy. Virtually everyone seeks health care at some point in his or her life, and because of the unique importance of health, more is expected of all entities and individuals in the health care system, including manufacturers and suppliers of medications and medical devices, to ensure the safety of their products. Yet the majority of pharmaceutical companies are publicly traded and for most companies, generating profit is an important and reasonable priority. This creates substantial tension for the leaders of pharmaceutical companies.

Despite these challenges, several options are available to pharmaceutical companies to help restore credibility and trust in their sponsored research.

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First, although companies that sponsor biomedical research studies can be involved in designing clinical studies, the data analysis should be performed by academic investigators who are not employed by the company sponsoring the research. Indeed, many academic groups who conduct industry-supported research insist that an academic faculty statistician without any financial interest in the study outcome conduct the analysis. In 2 recently published industry-sponsored studies, funded by Merck and by Novartis, the data analyses were, respectively, performed independently by the academic investigators or replicated by an independent academic statistician.

Second, preparation of the manuscript reporting the study results should primarily be the responsibility of the academic investigators, especially with respect to the initial drafts of the paper, which establish the frame and tone of the article, both of which are difficult to change after a first draft has been prepared. For pharmaceutical companies that provide writing assistance (or other support) for the preparation of manuscripts reporting the results of studies they sponsor, the roles, responsibilities, contributions, and identities of all persons involved with the manuscript should be reported in detail. A number of journals carefully detail the involvement of medical writers in the preparation of manuscripts.

Third, data from clinical trials could be made publicly available to qualified investigators for analyses of important research questions. GlaxoSmithKline recently announced plans to make raw data from clinical trials available to researchers. In addition, the European Medicines Agency plans to provide access to all clinical trial data sets submitted by industry in applications for new product registration. Although it will be important to monitor how these approaches to data sharing are implemented, how the data are used, and how the outcomes of the analyses based on these data are reported and applied, this initiative appears to have promise in promoting transparency for industry-sponsored research. Just as data sharing should become the norm for industry-supported trials, it should also be considered for all research, regardless of the funding source.

Fourth, the pharmaceutical industry could collectively agree to refrain from direct-to-consumer advertising for some specified period after a drug is approved or until postmarketing studies are completed. The FDA may require, at the time of drug approval or after approval, postmarketing studies or clinical trials “to assess a known serious risk related to the use of the drug, to assess signals of serious risk related to use of the drug, or to identify an unexpected serious risk when available data indicate the potential for a serious risk.” However, an important proportion of these studies are not completed in a timely fashion, particularly for drugs approved on the basis of surrogate end points. Without rigorous postmarketing studies, the true risk and safety profile of a drug in the “real-world” patient population is not defined. Voluntarily limiting direct-to-consumer advertising until postmarketing studies are completed would send an important signal that pharmaceutical companies are prioritizing patient safety, and may help to prevent some of the legal actions that result from rare, but serious, adverse events that were not detected in the initial trials. While direct-to-consumer advertising is illegal in most countries, and it would be difficult from a competitive standpoint for any single company to refrain from such advertising, as a group, despite their legal protection in the United States, pharmaceutical companies could modify how they approach this form of advertising.

Although other solutions also could help restore confidence in the pharmaceutical industry, the suggestions offered in this editorial are intended to help address some of the critical issues related to data analysis and presentation that have contributed to the erosion of trust in pharmaceutical industry research. In addition, 3 of these suggestions are already being implemented by some pharmaceutical companies. If integrity and trust in industry-sponsored research are restored, and rigorous studies demonstrate that a new product substantially improves the health of patients, physicians will be more likely to have confidence in prescribing that product, and none of the recommendations will hinder its sales.

Many of the great breakthroughs in medicine over the past 20 years are a result of the irreplaceable commitment to and investment in research by the pharmaceutical industry. Many outstanding scientists and clinicians who work in the pharmaceutical industry have made major contributions to improving the health and well-being of patients. But today the world is a very different place than it was in the past, and some physicians and the public, at least for now, are skeptical about the credibility of industry-sponsored research. Taking critical steps to enhance trust and confidence in companies that sponsor clinical research should help enable the pharmaceutical industry to thrive and, in doing so, continue to provide important products that improve health.

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REFERENCES
Antibiotics for Skin Infections
New Study Design and a Step Toward Shorter Course Therapy

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In this issue of JAMA, Prokocimer et al1 present the results of ESTABLISH-1 (Efficacy and Safety of 6-day Oral Tedizolid in Acute Bacterial Skin and Skin Structure Infections vs 10-day Oral Linezolid Therapy), an international, multicenter, double-blind, phase 3, noninferiority trial comparing a 6-day course of oral tedizolid phosphate once daily with a 10-day course of oral linezolid twice daily for treatment of acute bacterial skin and skin structure infections (ABSSSIs). Among 667 adults with ABSSSIs randomized to treatment with tedizolid phosphate (n = 332) or linezolid (n = 335), the early clinical treatment response rates were 79.5% with tedizolid phosphate and 79.4% with linezolid, a treatment difference of 0.1% (95% CI, −6.1% to 6.2%). The sustained clinical treatment response rates at the end of treatment (day 11) were 69.3% with tedizolid phosphate and 71.9% with linezolid (a treatment difference of −2.6% [95% CI, −9.6% to 4.2%]), with the lower bounds of the 95% confidence intervals within the prespecified 10% noninferiority margin. The authors concluded that tedizolid phosphate was statistically noninferior to linezolid in achieving early clinical response after initiating therapy for ABSSSI.

Many antimicrobials are efficacious for the treatment of bacterial skin infections, including those caused by methicillin-resistant Staphylococcus aureus (MRSA). Each has substantial limitations including toxicity, resistance, or the lack of an oral formulation. Tedizolid, an oxazolidinone like linezolid, is an orally available, highly bioavailable antibiotic that can be administered once daily. It has excellent in vitro activity against gram-positive organisms causing ABSSSIs, including linezolid-resistant S aureus; preliminary safety studies suggested it may have a better adverse effect profile than linezolid.

The strengths of the study by Prokocimer et al1 include its double-blind, double-dummy design; baseline stratification; careful definition of eligible infection types; criteria for skin lesion size measurement; specific response criteria of cessation of skin infection spread at the 48- to 72-hour assessment after therapy initiation; and minimal loss to follow-up. Much can be learned from the current study about the appropriate use of antibiotics for treatment of these common infections, and the design of future trials for treatment of ABSSSI.

Predominantly younger male outpatients were studied, more than one-third of whom were current or recent intravenous drug users. Infection types included cellulitis, major cutaneous abscess, and wound infections. Median infection area was larger than that seen in earlier trials of agents for ABSSSI.2 S aureus was the most commonly isolated pathogen, found in more than 80% of patients with a positive culture; MRSA was isolated from more than 40% of positive cultures.

Because antibiotics are so effective in treating ABSSSIs, which are associated with significant morbidity and mortality, placebo-controlled trials are not ethical; noninferiority trials have therefore become standard. In the primary efficacy analysis of this study, a short course of oral tedizolid once daily was noninferior to the standard 10-day

See also p 559.