PHARMACEUTICAL RESEARCH

Between Confidentiality and Scientific Exchange: The Place of Publication in Drug Discovery and Pharmaceutical Research

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To continue to improve life expectancy and quality of life, the discovery of innovative therapies should be among the prime goals of the life sciences. The large majority of the drugs that are discovered and successfully developed to the point of being used by patients come from the drug industry, but publications from this sector are rare among life sciences research publications. Publications in the field of pharmaceutical drug discovery should take into account the confidentiality inherent to the protection of the intellectual property rights of a discovery, but they are fundamentally important because they can enhance scientific knowledge, improve the care and safety of patients, provide information for prescribers, and educate the public about the pharmaceutical industry.

INTRODUCTION

The decision to publish in the pharmaceutical industry is influenced by two forces pulling in opposite directions (Fig. 1). On one side, there is a need to protect intellectual property (IP) rights related to innovation. On the other side, there is a drive to publish and share discoveries with the scientific community. The pharmaceutical industry is characterized by the lengthy, risky, and extremely expensive nature of drug development. It relies on patent protection to recoup the costs of the risks of innovative drug development. Patent protection and the associated secrecy are therefore the main incentives to continued innovation (1). However, scientists have the desire to publish their work, establish their role in the discovery, be evaluated by peers, and elicit feedback from other scientists.

The process of modern drug discovery and translational medicine generally adopts the “magic bullet” theory of Paul Ehrlich (1906), by which a drug is discovered by selectively targeting a system involved in pathology while leaving intact the surrounding environment (2). The process of drug discovery involves many steps, most of which are subsequent to those included in IP protection, and the failure rate is high at each step. If the challenge of bringing any product from invention to the market is high in all fields—the so-called “valley of death” (3)—the difficulty is particularly great in the drug industry. During this process, how do industry scientists decide what, why, and when to publish?

WHAT TO PUBLISH?

During the course of a drug discovery project, results from two main areas of research are amenable to publication. The first area is related to research on new potential targets. Relevant discoveries might encompass the finding of a new role for a peptide, an up-regulation of a substrate or a receptor in a disease, or a gene mutation causing activation or loss of function of a particular protein or pathway. The resulting papers are generally published in journals covering the areas of physiology, medicine, or more specific areas of research. The second area relates to publications about new drugs and might describe the discovery of previously unknown molecules or modes of therapy—antisense RNA, gene or cell therapy, vaccine—and their pharmacology. Additional papers might describe the drug’s pharmacokinetics, toxicology, and route of production. These publications appear in journals of pharmacology or other journals of the pharmaceutical arena. Alternatively, the manuscript might describe the progression of the drug discovery project from its starting point (oftentimes an academic publication) to the molecule selected as the drug, or the role of the endogenous system targeted by this molecule that is revealed by its use in animal or cellular models. Because “druggable” targets are often tackled
simultaneously by several pharmaceutical companies, the first scientific communication will often rapidly trigger a series of publications by scientists from the pharmaceutical industry or at universities.

The disclosure of clinical trial results is regulated by rules issued by health authorities, especially the European Medicines Agency and the U.S. Food and Drug Administration (FDA). Under FDA guidance, disclosure is mandatory for Phase II to IV results involving drugs already registered (granted marketing approval) (4). In contrast, there is little regulation of publications about preclinical research, early clinical studies, and studies on nonregistered molecules. All relevant pharmacology, safety, and toxicology data must be progressively added to the regulatory dossier of a drug in development—for example, to the Investigational New Drug Application in the United States—but no obligation exists in terms of making information available to the public until the product is approved. One could argue that safety findings relevant to a new class of drugs should be subject to obligatory disclosure, but the difficulty of proving an association between mechanism and effect might prevent exploration of valid principles by other companies.

WHY PUBLISH?

Why publish despite the pressure of confidentiality inherent to invention (5)? Information once published will be used by other pharmaceutical companies, as it proposes new ideas in research or reveals competitive information about a molecule. However, the motivation of the scientist to discover and share the discovery coincides with the interest of the pharmaceutical company. The information is distributed to the scientific world, to future users, to the media, and possibly to investors. Such scientific publications can serve to gauge the internal drug discovery research effort. For full papers, the principle of peer review offers a validation of the work realized in the labs. For conference abstracts, which should optimally only be submitted when a full manuscript intended for peer review is nearly finished, the exchange of information by oral communication or poster presentation provides the researcher and the company a benchmark to judge the work performed and generates new ideas and collaborations that will advance knowledge. However, pharmaceutical research often explores a new pathway vertically using multiple technologies, from molecular biology and chemistry to computer-assisted molecular modeling and pharmacology techniques, and abstracts may not be the optimal tool to communicate about this complex research.

Scientific publications also help to increase the appropriateness of drug prescriptions by physicians once the drug is on the market. Medical documentation driven by high-quality science allows a doctor to make his or her own judgment about the drug's potential, its risks, and the possibility of co-administration with other drugs. To increase knowledge about a newly described molecule, a duty of phama is to share not only the information about the molecule but also the molecule itself. The fully integrated business model adopted in the past by large pharmaceutical companies is not sustainable anymore (6). By allowing academic laboratories to gain access to the molecule, perform their own research, and publish their own work, the pharmaceutical industry gains in understanding of the strengths and weaknesses of their drugs and in credibility. Vice versa, the scientists from the external world act as independent consultants who contribute to the evaluation of the drug.

Publications should describe not only the efficacy but also the safety aspects of the drug. To ensure the safety of patients, the promise of the pharmaceutical industry to health authorities rests solely on the obligation to transmit all relevant safety information to the regulatory dossier, not necessarily to publish it. However, the work that will have been done to understand a side effect and to explain the mechanism of this side effect and its relevance for patients at therapeutic concentrations should be published in manuscripts. Such publications will ensure a better understanding of the drug's profile and handling. Overall, publications complement the official label, which is agreed upon with health authorities. However, the risks of biases in publications of research findings exist, and clearly point to an imbalance between the submission of efficacy and of safety studies and between the submission of studies with positive results and studies with negative or nonsignificant results, which are less likely to be published (7–9). In the current era of risk minimization (10), biases also exist in the way manuscripts are evaluated by editors, in that side effects can be published on the basis of single cases, whereas more stringent data may be necessary for publications describing a molecule's benefit. Similarly, meta-analyses are more easily judged as valid when they describe a risk versus a benefit.

Publications of high-quality science should also help the pharmaceutical industry gain positive recognition. This industry is often criticized for the potential conflict between patient welfare and profits. More visibility will increase the understanding of the process of drug discovery, the focus on finding treatments for diseases with high unmet medical needs, and the major risks taken by companies in their innovative research. A culture of high-level scientific publications from a drug discovery department reflects transparency, creativity, and teamwork and encourages researchers to innovate. Good publications in turn support the recruitment of post-doctorals, academic researchers, and highly competent experts. The quality of publications will also guide the decisions made by potential investors in start-up biotech companies. A contrario, the consequences of not publishing are multiple: (i) a lack of sharing of the scientific background that supports the development of a new drug, (ii) deficient communication about initiatives that are important to public health, (iii) a lack of information for future clinical investigators, (iv) a reduction in the enrichment of science afforded by the exchange of knowledge, (v) a lack of visibility of the research activities of the company, and (vi) failure to fulfill scientific and ethical obligations.

Publications in the pharmaceutical industry are a voluntary act that is not mandatory, not the “primum movens” of this research, in contrast to university research in which publications are the ultimate goal. Publication records, which serve as the sole measure of success in academia, can also gauge the quality of research and development in the pharmaceutical industry. However, particular difficulties are associated with publications stemming from the pharmaceutical industry. The first hurdle is the obligation to announce a conflict of interest. Is a salary from a drug discovery company more prone to elicit a biased behavior than an academic salary? Or is a company affiliation a disadvantage for a scientist submitting a publication to a journal? Another issue, after a paper from pharmaceutical research has been submitted, lies in the choice of the right reviewers.
WHEN TO PUBLISH?

In planning the best timing for publication in the pharmaceutical industry, the need to secure the IP rights must be considered first. Before any paper is submitted for publication, the authors should determine whether it describes an invention that should be protected by a patent application. The 18-month period between the filing date of a patent application and the date when the patent is published and made available to the public is often used to prepare a first publication on the invention so that the first paper and publication of the patent application are simultaneous. This period will satisfy the legitimate desire of the company to preserve a period of secrecy in order to maintain its advantage in a discovery.

An important element for optimizing the timing of publication is the clinical confirmation of a preclinical concept. The scientific value of a discovery is multiplied when the translational science applied to this new medication is confirmed by positive results in clinical trials. Therefore, an argument can be made that the first publication of laboratory discoveries should happen after proof-of-concept or Phase II trials.

CONCLUSION

The public is prompt in judging the negative side of industrial drug firms, their high profit margins, the David and Goliath perception of the class action suits against pharmaceutical companies, and the revelations about drug withdrawals because of safety concerns. Much work is needed to elevate the quality and density of publications from pharmaceutical research, the more likely it will be to have a paper appreciated by the reviewers and have a fair chance to reach from laboratory research to human trials—perhaps the ideal scenario.

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