

DRUG DISCOVERY

Repurposing with a Difference

Mark S. Boguski,^{1*} Kenneth D. Mandl,² Vikas P. Sukhatme³

There is widespread belief that current models of drug discovery and development need revamping and reinvention in order to make pharmaceutical research and development (R&D) more predictable, reliable, and less costly. We suggest a novel approach to this challenge that involves profound changes in the way post-marketing surveillance data are gathered and used. This approach capitalizes on recent advances in molecular medicine, human genomics, and information technology, as well as an increasingly sophisticated public eager for solutions to their unmet medical needs. Novel business models and imaginative legal and regulatory reforms will be critical to fulfill this promise and to maximize its impact.

Despite enormous investments in basic science, technology development, and experimentation with new organizational and management structures, pharmaceutical product development still requires at least 10 to 15 years and costs between \$500 million and \$2 billion (1, 2). Furthermore, there is a widening productivity gap: Research and development spending continues to increase, yet the number of new therapeutic chemical and biological entities approved by the U.S. Food and Drug Administration (FDA) has been declining since the late 1990s (3). Overcoming these and other obstacles to increased productivity may require an overhaul of the R&D paradigm (4); some have called for a “disruptive” transformation of the industry (5).

One response to the productivity gap is drug “repurposing” (6, 7) or “repositioning” (8)—terms that refer to the identification and development of new uses for existing or abandoned pharmacotherapies. New uses of existing drugs cost much less to develop compared with de novo drug discovery and development (8). There are a

number of remarkable examples of repurposed drugs whose additional indications were discovered serendipitously (8). For instance, bupropion (Wellbutrin) was originally developed to treat depression but found another use in smoking cessation (marketed as Zyban for this indication). Duloxetine (Cymbalta) was also developed to treat depression, but was hypothesized—based on mechanism of action, not serendipity—as a treatment for stress urinary incontinence. It was successfully developed and marketed for both indications.

A very unusual case of repurposing (the rescue of an abandoned drug) is thalidomide. Originally developed as a treatment for morning sickness during pregnancy, its dan-

Consumer activism, genetic information, and social networking technologies are creating many opportunities for drug repurposing.

gerous side effects became tragically evident in the late 1950s and early 1960s only after an epidemic of severe birth defects occurred in children exposed to the drug in utero (9). Thalidomide was withdrawn from the market but, several years later, was accidentally discovered to be uniquely effective in treating severe complications of leprosy. It is now marketed for this use under the trade name Thalomid. Twenty years later, Thalomid's use was granted a new method-of-use (MOU) patent (see below) as a treatment for a type of cancer (multiple myeloma).

Another form of repurposing is the off-label use of prescription medications to treat a condition other than that for which the drug was approved by the FDA (10). This is possible and common, because the FDA regulates how drugs are approved but not how medicine is practiced; physicians are free to prescribe approved drugs for any uses they see fit, provided they have exhausted “standard-of-care” approaches and have reason to believe that the off-label use will be of clinical benefit. Because of our increasingly sophisticated understanding of human biology and the molecular pathways of disease, one would expect there to be increasing opportunities for expanding off-label use based on fully elucidated pathways and mechanisms of action, a situation that has been called a “new grammar of drug discovery” (11). A classic example of this phenomenon is imatinib (Gleevec and Glivec), a drug originally developed to treat chronic myelogenous leukemia whose indications were expanded to other cancers on the basis of common underlying molecular pathways (11, 12).

A more systematic way to explore the potential of existing drugs for repurposing would involve a new use of postmarketing surveillance information. Postmarketing safety monitoring (13) is regulated by the FDA in the United States and the European Medicines Agency in Europe (14, 15). The detection of potential adverse drug reactions has traditionally depended on voluntary and spontaneous reporting by individual patients and physicians, using the FDA's Adverse Events Reporting Systems (AERS). Also, pharmaceutical companies monitor the literature for case reports that may indicate a safety problem with their medicines. In addi-



More than one use. Prior examples of repurposed drugs include bupropion and thalidomide (8). A more systematic approach involving postclinical-trial patient data could yield many more repurposed drugs.

¹Department of Pathology, Beth Israel Deaconess Medical Center and Center for Biomedical Informatics, Harvard Medical School, 10 Shattuck Street, Boston, MA 02115, USA. ²Children's Hospital Informatics Program at Harvard-MIT, Division of Health Sciences and Technology and Center for Biomedical Informatics, Harvard Medical School, Boston, MA 02115, USA. ³Beth Israel Deaconess Medical Center and Department of Medicine, Harvard Medical School, Boston, MA 02115, USA.

*To whom correspondence should be addressed. E-mail: mark_boguski@hms.harvard.edu

tion, more proactive approaches, such as statistical data-mining of hospital records, are beginning to emerge (16–19).

An increasingly important and influential resource is groups of patients who can access medical information on the Internet and see themselves as equal partners with—if not the primary drivers of—the medical profession in managing their health (20). Special online resources, such as Resounding Health, have recently been developed to serve this population. In a growing number of cases, patients or their relatives not only initiate, but also design and carry out, research programs that have, for example, advanced understanding and treatment of gastrointestinal stromal tumor, gastroesophageal reflux disease, autism, and the genetic disorder pseudoxanthoma elasticum (20). Most such efforts to date have been carried out as part of a “gift economy,” in which patients and their families volunteer time and effort to bypass what they consider the “lethal lag time” of professional research processes and formalisms (20).

Such efforts are aided by the fact that consumers can now have their genomes typed for disease associations for as little as \$399 and can share these data electronically with their families, friends, or self-defined networks of individuals (21). A notable recent case is that of Google cofounder Sergey Brin, whose commercial genome scan revealed a high risk of developing Parkinson’s disease. Brin is personally funding a study of 10,000 patients through two nonprofit companies, including the Michael J. Fox Foundation for Parkinson’s Research (22).

Disease-oriented social networks, such as Genetic Alliance, PatientsLikeMe, and MyDaughtersDNA, have created online communities to advance the translation of research into new treatments. Google Health, Microsoft HealthVault, and Indivo (deployed by the Dossia consortium of employers) have created personally controlled, electronic health records for individuals or groups to share their medical conditions with health care providers, researchers, and others (23). This convergence of increasing consumer activism, along with access to genetic information services and sophisticated, advanced, and accessible information technologies, has created unprecedented opportunities to bring worldwide human resources and data to bear on biomedical research problems.

Whereas the purpose of classical pharmacovigilance is to identify adverse side effects of drugs (13), the new kind of pharmacovigilance we envision aims to detect, assess, and understand beneficial drug side effects (or expanded drug indications) that may become

apparent during their development or use. This “type 2” pharmacovigilance could be carried out, for example, by professionals using data-mining methods to look for potential beneficial events in electronic health records (16). However, we also anticipate another approach, in which potential beneficial side effects of existing drugs are identified by online communities of drug consumers using social networking technologies in a process that has been called “crowdsourcing” (24, 25). Potential beneficial side effects (or new indications) for existing drugs identified in this way could be assessed in a manner conceptually similar to the formal methods by which causality criteria are applied to adverse events (15). Following initial assessment, candidates would be prioritized for further investigation, including some form of clinical trials. Validation would be most straightforward for those phenomena that could be rationalized on the basis of known disease pathways or mechanisms of action. Potential new uses that are not consistent with known disease mechanisms might generate hypotheses that could lead to the discovery of new biological processes or disease pathways.

Definitive clinical trials for novel uses of existing drugs will remain costly, and pharmaceutical companies are reluctant to invest in such efforts without patent protection. New information about the uses of existing drugs may create intellectual property in the form of MOU patents as opposed to composition-of-matter (COM) patents. COM patents are generally considered to be more valuable than MOU patents, but this differential valuation may be changing because, as Eisenberg points out, “Drugs are information-rich chemicals that in many respects are more akin to other information products (such as databases) than they are to other chemicals” (26).

Classical pharmacovigilance, which is exclusively focused on safety issues, can produce information that is of considerable social value for patients, physicians, and insurers at the expense of economic value to pharmaceutical companies (26). Thus, repurposed pharmacovigilance that is focused on beneficial new uses will need to be based on new business models [such as open-sourcing (27)] apart from the traditional, vertically integrated R&D enterprise (5). It would also be enabled by either patent reform by Congress or new doctrinal interpretations of current law by the FDA and the courts, as has already been suggested (28).

Our proposal, to repurpose pharmacovigilance, outlines a new approach to drug and

biomarker discovery and suggests ways of overcoming the inadequate incentives of current business models and regulatory regimes that contribute to the productivity gap in pharmaceutical R&D. This approach leverages the talents, motivations, and resources of individuals and groups whose unmet medical needs are the fundamental goals of developing new therapies.

References and Notes

1. C. P. Adams, V. V. Brantner, *Health Aff. (Millwood)* **25**, 420 (2006).
2. J. A. DiMasi, R. W. Hansen, H. G. Grabowski, *J. Health Econ.* **22**, 151 (2003).
3. H. Grabowski, *Pharmacoeconomics* **22**, 15 (2004).
4. K. I. Kaitin, *Clin. Pharmacol. Ther.* **83**, 210 (2008).
5. C. M. Christensen, J. H. Grossman, J. Hwang, *The Innovator’s Prescription: A Disruptive Solution for Health Care* (McGraw-Hill, New York, 2009).
6. D. W. Carley, *IDrugs* **8**, 306 (2005).
7. D. W. Carley, *IDrugs* **8**, 310 (2005).
8. T. T. Ashburn, K. B. Thor, *Nat. Rev. Drug Discov.* **3**, 673 (2004).
9. W. G. McBride, *Lancet* **278**, 1358 (1961).
10. K. R. Loughlin, J. A. Generali, *The Guide to Off-Label Prescription Drugs: New Uses for FDA-Approved Prescription Drugs* (Simon & Schuster, New York, 2006).
11. M. C. Fishman, J. A. Porter, *Nature* **437**, 491 (2005).
12. D. Vasella, R. Slater, *Magic Cancer Bullet: How a Tiny Orange Pill May Rewrite Medical History* (HarperCollins, New York, 2003).
13. World Health Organization (WHO), *The Importance of Pharmacovigilance: Safety Monitoring of Medicinal Products* (WHO, Geneva, 2002); <http://apps.who.int/medicinedocs/en/d/Js4893e>.
14. E. G. Brown, L. Wood, S. Wood, *Drug Saf.* **20**, 109 (1999).
15. H. S. Rehan, D. Chopra, A. K. Kakkar, *Eur. J. Intern. Med.* **20**, 3 (2009).
16. J. S. Brownstein et al., *PLoS One* **2**, e840 (2007).
17. L. Harmark, A. C. van Grootheest, *Eur. J. Clin. Pharmacol.* **64**, 743 (2008).
18. M. Hauben, A. Bate, *Drug Discov. Today* **14**, 343 (2009).
19. J. Weaver, M. Willy, M. Avigan, *AAPS J.* **10**, 35 (2008).
20. T. Ferguson, *e-Patients: How They Can Help Us Heal Healthcare* (2007); www.e-patients.net/e-Patients_White_Paper.pdf.
21. M. S. Boguski, in *Genomic and Personalized Medicine*, H. F. Willard, G. S. Ginsberg, Eds. (Elsevier, San Diego, CA 2009), pp. 252–257.
22. A. Pollack, *New York Times*, 12 March 2009; www.nytimes.com/2009/03/12/business/12gene.html?emc=eta1.
23. K. D. Mandl, I. S. Kohane, *N. Engl. J. Med.* **358**, 1732 (2008).
24. J. Howe, *Crowdsourcing: Why the Power of the Crowd Is Driving the Future of Business* (Crown Business, New York, 2008).
25. C. Li, J. Bernoff, *Groundswell: Winning in a World Transformed by Social Technologies* (Harvard Business, Boston, 2008).
26. R. S. Eisenberg, *Yale J. Health Policy Law Ethics* **5**(2), 717 (2005).
27. B. Munos, *Nature Rev. Drug Discov.* **5**, 723 (2006).
28. B. N. Roin, *Texas Law Rev.* **87**, 503 (2009).
29. M.S.B. is a former vice president of the Novartis Institutes for Biomedical Research and the founder of Resounding Health Inc. K.D.M. is a principal developer of Indivo, an open-source, personally controlled health record that has been deployed through Dossia, Inc. V.P.S. is a cofounder of GlobalCures Inc.

10.1126/science.1169920