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Open Source Drug Development: A Path to More Accessible Drugs and Diagnostics?

Emily Marden*

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I. INTRODUCTION: IS OPEN SOURCE LICENSING OF PATENTS A SOLUTION TO DRUG COSTS AND ACCESS?

The high cost of medicines and resulting lack of access to many of these treatments represent some of the most troubling issues of our time and are the subject of much attention both in the developed—and the developing—world.¹ There can be no doubt that biomedical science continues to make breakthroughs in the treatment of many diseases. Indeed, in the last twenty-five years, treatments for chronic conditions such as HIV infection, diabetes, and cardiovascular disease have been developed and widely adopted by health care providers.² Yet, globally—and even within the U.S.—these pharmaceutical treatments are not always available to or utilized by those who need them because of their high costs.³

Patents have been widely identified as being at least one of

1. See, e.g., Diane V. Havlir & Scott M. Hammer, *Patents Versus Patients? Antiretroviral Therapy in India*, 353 *NEW ENG. J. MED.* 749 *passim* (2005); Mary Moran, *A Breakthrough in R&D for Neglected Diseases: New Ways to Get the Drugs We Need*, 2 *PLOS MED.* 0828, 0828 (2005); Yochai Benkler, *Commons-Based Strategies and the Problems of Patents*, 305 *SCIENCE* 1110 *passim* (2004); Bernard Pécoul, *New Drugs for Neglected Diseases: From Pipeline to Patients*, 1 *PLOS MED.* 019, 019 (2004); Patrice Trouiller et al., *Drug Development for Neglected Diseases: A Deficient Market and a Public-Health Policy Failure*, 359 *LANCET* 2188, 2188–91 (2002).

2. J.D. Kleinke, *The Price of Progress: Prescription Drugs in the Health Care Market*, *HEALTH AFF.*, Sept.–Oct. 2001, at 43.

3. See, e.g., Stephanie Saul, *In Sour Economy, Some Scale Back on Medications*, *N.Y. TIMES*, Oct. 22, 2008, at A1, available at <http://www.nytimes.com/2008/10/22/business/22drug.html>; John D. Piette et al., *Cost-Related Medication Underuse Among Chronically Ill Adults: The Treatments People Forgo, How Often, and Who is at Risk*, 94 *AM. J. PUB. HEALTH* 1782 *passim* (2004).

the causes of the problem.⁴ Patents give their owners a legal monopoly and grant a right to exclude others from use of an invention. As such, the patent holder can charge a fee for a license to use the patent. The pharmaceutical industry generally characterizes these amounts charged as reasonable, in light of very large research and development costs.⁵ The argument is that intellectual property (IP), in the form of patents, provides the incentive to invest in the risk-laden drug development business.⁶

Others maintain that the financial benefit reaped by pharmaceuticals is out of proportion with the cost to society as a whole in terms of high prices and lack of access to health care innovations.⁷ They further question the notion that patents are necessary for innovation.⁸

For some, the solution to this impasse is a change to the way IP rights—and patent rights in particular—are exercised. In particular, it is now increasingly common to point to open source, modeled on non-proprietary models used in the computer software arena, as a mode of IP practice that can at once make IP more widely accessible and by implication can lower the costs of drugs. In her 2008 book, *Biobazaar*, Janet Hope effectively sets the bar for this discussion:

A key premise of this book is that open source principles of technology development, licensing, and commercial exploitation offer at least a partial solution to the innovation lock-down caused by extensive private control over scientific and technological information within a

4. See, e.g., Stephen M. Maurer et al., *Finding Cures for Tropical Diseases: Is Open Source an Answer?*, 1 PLOS MED. 183, 183 (2004); see also John E. Sulston, Chair, Inst. for Sci., Ethics and Innovation, Who Owns Science (May 19, 2009) (see <http://www.terry.ubc.ca/index.php/2009/04/30/who-owns-science-sir-john-sulston-on-may-19th>); Jean O. Lanjouw, *Patents, Price Controls, and Access to New Drugs: How Policy Affects Global Market Entry passim* (The National Bureau of Economic Research, Working Patent No. 11321, 2005), available at <http://www.nber.org/papers/w11321>.

5. Henry Grabowski, *Patents, Innovation and Access to New Pharmaceuticals*, 5 J. INT'L ECON. L. 849 (2002).

6. See, e.g., Lila Feisee, Biotech. Indus. Org.'s Dir. for Fed. Gov't Relations & Intellectual Prop., Anything Under the Sun Made by Man (April 11, 2001), available at <http://www.bio.org/speeches/speeches/041101.asp> (pointing to, for instance, the explosion of the biotechnology industry following the Supreme Court's decision in *Diamond v. Chakrobarty*, 447 U.S. 303 (1980), which declared that genetically engineered bacteria were patentable, as evidence of the power of patents to stimulate innovation).

7. See MICHELE BOLDRIN & DAVID K. LEVINE, AGAINST INTELLECTUAL MONOPOLY 213–14 (2008).

8. *Id.* at 215.

highly concentrated industry structure.⁹

There are those who take the concept further and have proposed an open source approach in biology as a means toward ongoing access to knowledge that results in less costly, more widely available health care products. Thus, for example, Stephen M. Maurer and his colleagues propose an open source system in which “volunteers [would] use a variety of computer programs, databases and computing hardware” to share ideas that have not been patented and hence to develop lower cost pharmaceutical products.¹⁰ Maurer and his colleagues go on to promise that “open-source drug discovery is feasible” and invite scientists to make the model work explicitly, in this case, for developing drugs for tropical diseases.¹¹ Kathleen M. Nolan-Stevaux argues similarly that an open source approach to biology is the best incentive—versus other IP alternatives—to stimulate drug development with the aim of improving access in the developing world.¹² The aim, again, is to embrace an alternative to conventional patent rights to allow simultaneously (1) a model of contribution and open participation in innovation and (2) an approach to drug development that does not allow for the monopoly rents imposed by patent exclusivity.¹³

There have been some efforts in this area. In the context of neglected tropical diseases, the Tropical Disease Initiative (TDI)¹⁴ focuses its efforts on coordinating charities to create nonprofit venture-capital firms in the guise of “Virtual Pharmas” to search out and develop promising treatments.¹⁵ The TDI intends to play the role of a “kernel” in this process and provides a platform for scientists from laboratories, universities, institutes, and corporations to collaborate in order

9. JANET HOPE, BIOBAZAR: THE OPEN SOURCE REVOLUTION AND BIOTECHNOLOGY 20 (2008).

10. Maurer et al., *supra* note 4, at 185.

11. *Id.*

12. Katherine M. Nolan-Stevaux, *Open Source Biology: A Means to Address the Access & Research Gaps*, 23 SANTA CLARA COMPUTER & HIGH TECH. L. J. 271 (2007).

13. *Id.*

14. Tropical Disease Initiative, <http://tropicaldisease.org/> (last visited Oct. 20, 2009).

15. Maurer et al., *supra* note 4, at 183.

to find new drugs to treat neglected tropical diseases.¹⁶ The idea is that all knowledge is shared and not patented and that contracts will be awarded by TDI at some point to put the drugs through the clinical testing process.

In addition, Open Source Drug Discovery (OSDD) is funded by the Government of India to provide an open source platform for aggregating scientific knowledge in order to discover drugs to treat diseases that are prevalent in the developing world with the aim of providing affordable healthcare to people around the world, particularly in developing countries.¹⁷ These emerging platforms reflect the growing interest in open source as an alternative intellectual property mechanism that may ensure greater openness and access to information.

By the admission of all, these efforts represent first steps and open source drug development remains unproven as a strategy to reduce drug costs and to increase access. The aim of this article is to take the discussion of open source and drug development a step further and to rigorously test the hypothesis that has been proposed, namely that an open source drug development process offers a potentially realistic solution to the drug cost and accessibility issues. Toward this end, the present article asks what open source drug development would look like and whether it is likely to yield success on its own dual criteria of enabling ongoing innovation and increasing access of end products. This discussion draws on a rigorous analysis of the drug development process as well as the technical details of licensing patents on an open source basis.

Overall, the article concludes that open source is not a viable option for drug development if drug development is understood as being the process of moving a molecule, pathway, or process past drug discovery through to the approval of a

16. *Id.*

17. Open Source Drug Discovery, What is OSDD, <http://www.osdd.net/what-is-osdd> (last visited Oct. 20, 2009) [hereinafter OSDD]. The government of India has committed \$32 million to the OSDD project and released \$8.2 million. Much like the TDI, students, scientists, researchers, academics, institutions, and corporations from around the world may become partners in OSDD, where they can contribute to and synthesize available knowledge in order to discover new drugs. New molecular entities (NMEs) will not be patented, but instead will put into the public domain. With the aid of the Government of India or philanthropic funding, the development of drugs is to be outsourced to contract research organizations and other private industry partners. *Id.*

drug or diagnostic by regulatory authorities.¹⁸ It is indisputable that open source operates elegantly in the information technology context and has produced a number of widely used programs, even while preserving access to the underlying source code. Moreover, it is likely that in the drug discovery context and in very early development stages open source could succeed at keeping certain underlying intellectual property open and available for further innovation. As discussed below, however, it is not clear that full-scale open source drug development can yield less costly and more accessible drugs. Patent rights differ markedly from copyrights and the efforts that must be undertaken to make open source workable for drug compounds are difficult and expensive. Even if intersecting patent rights could be resolved, the legal and regulatory requirements of drug development make that process expensive and resource-heavy, whether or not open source plays a part in the process. Given all this, it cannot be maintained that an open source drug development system offers a better alternative than other models that have been proposed.

This article begins in Part II with a review of the origin of open source in the copyright context of the information technology arena. It then examines in detail how open source might operate with respect to patents, the form of intellectual property generally used for compounds in drug development.¹⁹ In so doing, it points to two aims that have been identified for using open source with respect to patents: (1) to preserve access

18. See University of California, San Francisco, School of Pharmacy Glossary, <http://pharmacy.ucsf.edu/glossary/d/> (last visited Oct. 20, 2009) (defining “drug development” and “drug discovery”). “Drug discovery” refers to the research process that identifies molecules with desired biological effects and selects them as having promise as new therapeutic drugs in humans.

19. The public discussion of open source for drug development variously refers to open source genomics and open source biotechnology. Biotechnology is an industry that commercializes biological compounds. Genomics, in turn, characterizes a broad field of study, comprised of anything having to do with the genome. As such, it also characterizes biological compounds. The goal of this article is to examine the potential use of open source for active compounds that might be patented and used in drug development; these could be derived from the study of genomics or could be chemical compounds. For this reason, this article refers to compounds used in drug development, with the understanding that this could describe a range of types of materials.

to the information,²⁰ thus fostering the possibility of an open system of innovation and ongoing fruitfulness of research,²¹ and (2) to yield products that are less costly and more accessible.²² In order to test the open source concept in drug development, the article goes on to present a detailed overview of what is entailed in that process following the discovery stage, right through to clinical trials, approval and post-marketing obligations.²³ This article then turns, in Part III, to the topic of what an open source drug development process might be, how open source licensing provisions might play out, and how development could be undertaken even in the absence of a large pharmaceutical company sponsor.

Part IV examines the question: would use of an open source licensed compound in the drug development process likely meet the complementary goals of preserving access to the fundamental innovation and yielding a product that is more accessible and less expensive? A further issue considered is whether public or private enterprises would want to engage open source drug development, given the potential impacts. In reaching findings on these issues, the article concludes in Part V with suggestions of other alternatives that offer potentially more viable options for reigning in the costs of drug development and resulting prices for pharmaceutical products.

II. OPEN SOURCE: BACKGROUND AND OPERATION

A. HISTORY OF OPEN SOURCE: ROOTS IN INFORMATION TECHNOLOGY/SOFTWARE

Open source—and its precursor in the information technology community, GNU—was developed in response to the commercial software industry's IP practices.²⁴ As a general principle, software is primarily written in code which, as a

20. Although the fundamental rationale underlying patents is that the owners are granted a limited monopoly in return for making their discoveries public, in practice the intellectual property system does provide a degree of control over information and can be said to limit access.

21. See, e.g., HOPE, *supra* note 9, at 151–54.

22. See, e.g., BOLDRIN & LEVINE, *supra* note 7, at 225–26.

23. See University of California, San Francisco, School of Pharmacy Glossary, *supra* note 18 (discussing stages of drug discovery).

24. FREE SOFTWARE, FREE SOCIETY: SELECTED ESSAYS OF RICHARD M. STALLMAN 157–68 (Joshua Gay ed., 2002) [hereinafter STALLMAN: SELECTED ESSAYS].

written form, is subject to IP coverage by copyright. A copyright allows the holder to prevent others from copying, distributing, or adapting the code.²⁵ The common practice in commercializing software is to require users to agree to a license before use, which bars the user from sharing or copying the software.²⁶

For a number of software innovators, the growing commercialization of software posed a barrier to ongoing innovation because it forced users to agree to a license for use and barred them from seeing or altering source code. The free software and open source movements grew out frustration with the practice of closing off programs as they developed, even to those who participated in their development at earlier stages.²⁷ Richard Stallman, and later Linus Torvalds (Linux), developed operating systems that would leverage the contributions of many while leaving the source code open to any and all contributors. Stallman termed his approach, “GNU” (which stands for “Gnu’s Not Unix”, a recursive acronym).²⁸ The Linux operating system, which was first released by Torvalds, represented a further development of GNU and became emblematic of the movement. Torvalds’s approach became known as “open source,” because of the availability of the source code.²⁹

Developers of the free software movement designed a copyright license which could help share programs and maintain open access to source code: this is the so-called General Public License (GPL) or “copyleft.”³⁰ The GPL was

25. 17 U.S.C. § 106 (2006).

26. Paul Goodman, *Shrink Wrap License Agreements: Unravelling Some of the Confusing Legal Issues*, 9 MACTECH (1993), available at <http://www.mactech.com/articles/mactech/Vol.09/09.03/Shrinkwrap/index.htm>.

27. STALLMAN: SELECTED ESSAYS, *supra* note 24, at 157–68; see also Free Software Foundation, <http://www.fsf.org> (last visited Oct. 27, 2009).

28. Richard Stallman, *The GNU Operating System and the Free Software Movement*, in OPEN SOURCES: VOICES FROM THE OPEN SOURCE REVOLUTION 2–3 (1st ed. 1999), available at <http://oreilly.com/catalog/opensources/book/copyright.html>.

29. See *id.* at 53. It is worth noting that the nomenclature and distinctions between these movements remains an issue of some debate. Richard Stallman, for example, is firmly against using “open source” as a description of a movement that includes GNU. *Id.*

30. SAM WILLIAMS, FREE AS IN FREEDOM: RICHARD STALLMAN’S CRUSADE FOR FREE SOFTWARE 128 (2002).

deemed necessary, because copyrights are otherwise self-executing.³¹ That is, just by writing a software program, it is deemed copyrighted; no further action is needed on the part of the programmer and a user is obligated not to copy the source code.³² The GPL is an affirmative rejection of this right. It publicly states that the source code is not copyrighted and is instead available to copy, change and freely distribute (thus the name “copyleft”).³³ The GPL is said to be viral because the license obligation applies to each subsequent licensee.³⁴

Collectively, these developments became known as open source, though there are a number of variant approaches.³⁵ As developed in the Linux context, supporters of the open source movement also believe that the more people working on a particular problem (or software design), the better.³⁶ The philosophy is that the greatest possible non-hierarchical collaboration can maximize the potential value and the potential benefit of a new idea. Thus, work is generally structured in a non-hierarchical—or bazaar-like—manner with the prototypical example of principle in action being the development of the Linux operating system. The number and abilities of programmers working on the product are not limited to those that exist within the boundaries of a single firm but rather include a diffuse network.³⁷

In the software sector, this novel approach has provided a successful platform for researchers and commercial enterprise. The internet, for example, relies on massive numbers of Linux

31. *See id.* at 122–23.

32. *Id.*

33. Free Software Foundation, GNU General Public License (version 3, June 29, 2007), <http://www.gnu.org/copyleft/gpl.html> [hereinafter GNU GPL].

34. *Id.*

35. Richard Stallman, President, Free Software Found., Lecture at the University of British Columbia: Free Software in Ethics and in Practice (Feb. 6, 2009) [hereinafter Stallman lecture]. There are disputes amongst the progenitors of these movements as to the correct terminology and whether “free software” is indeed synonymous with “open source.” Rather than weighing in on this discussion, I adopt the term “open source” to refer to the free and open source code that was the hallmark of the movement.

36. *See* Jae Yun Moon & Lee Sproull, *Essence of Distributed Work: The Case of the Linux Kernel*, in *DISTRIBUTED WORK* 381–404 (Pamela Hinds & Sara Kiesler eds., 2002).

37. ERIC S. RAYMOND, *THE CATHEDRAL AND THE BAZAAR: MUSINGS ON LINUX AND OPEN SOURCE BY AN ACCIDENTAL REVOLUTIONARY* 41 (1st ed. 1999).

servers (for Google, among other things).³⁸ Other open source based software companies have achieved financial success by: (1) selling a convenient package of products, some of which may be freely available, (2) consulting to other software companies, or (3) providing technical support for the program.³⁹ While the software may be available elsewhere for free, users (particularly non-programmers) may prefer to buy a product they trust from a source that strives to serve their needs. According to one commentator, IBM Corporation likely makes twice as much profit from its support of open source software (Linux based products) than from regularly licensed products.⁴⁰

B. OPEN SOURCE IN THE BIOTECHNOLOGY SECTOR

The aim of devising an open source approach for biotechnology and specifically drug development is similarly to create a system that will allow contributors and users greater freedom to use innovation in productive, more inclusive ways. As described by Janet Hope in her book, *Biobazaar: The Open Source Revolution and Biotechnology*:

Open source . . . is an attempt to renegotiate [the relationships in IP] based on (1) a reframing of intellectual property as a means of facilitating, rather than hindering, the production of knowledge as a public good and (2) the gradual transformation of biotechnology research and development practices toward the production of more convivial [user oriented, available] tools.⁴¹

Just as open source software was a reaction to the restrictions placed on programmers and users by proprietary practices in that sphere, the open source movement in biotechnology has arisen largely in response to concerns about the implications of patent use. In the biotechnology arena, these concerns include questions about the implications of

38. Amanda McPherson, *Linux is Everywhere (Now in the Air)*, LINUX FOUND., AMANDA'S BLOG (August 28, 2007, 6:07 AM), <http://www.linuxfoundation.org/node/2426>.

39. Examples of other open-source-based software companies are Apache HTTP Server, osCommerce, and Mozilla Firefox.

40. John Newton, *Professional Open Source Software*, JOHN NEWTON'S THOUGHTS, IDEAS AND OPINIONS ON CONTENT MANAGEMENT, ENTERPRISE SOFTWARE AND OPEN SOURCE, July 29, 2009, <http://newton.typepad.com/content/2009/07/professional-open-source-software.html>

41. HOPE, *supra* note 9, at 329.

ownership of biological materials⁴² for the practice of science,⁴³ and for research and access to ultimate end health care products.⁴⁴

Nonetheless, application of the open source approach to biotechnology is not a simple matter. There are important differences between software and health care products that make the transfer of the model complex as outlined briefly in the table on page 228.

42. With respect to IP, questions have long been raised about the ethics of allowing ownership of genetic material. See, e.g., LORI ANDREWS & DOROTHY NELKIN, *BODY BAZAAR: THE MARKET FOR HUMAN TISSUE IN THE BIOTECHNOLOGY AGE* *passim* (2001) (acknowledging concerns about the ethics of patenting). These concerns continue. See, e.g., John Conley, *The ACLU v. Myriad Genetics Suit: Legitimate Challenge or Publicity Stunt?*, GENOMICS L. REP. (June 4, 2009), <http://www.genomicslawreport.com/index.php/2009/06/04/aclu-v-myriad-genetics-suit-legitimate-challenge-or-publicity-stunt/>. The IP and ethics issue is an important one; however, it is not the focus on the present article.

43. See, e.g., JOHN SULSTON & GEORGINA FERRY, *THE COMMON THREAD: A STORY OF SCIENCE, POLITICS, ETHICS, AND THE HUMAN GENOME* (2002) (recounting the importance of open source in projects such as the Human Genome Project); Carl Shapiro, *Navigating the Patent Thicket: Cross Licenses, Patent Pools, and Standard Setting*, in 1 *INNOVATION POLICY AND THE ECONOMY* 119, 121 (Adam B. Jaffe et al. eds., 2000).

44. See, e.g., Michael A. Heller & Rebecca S. Eisenberg, *Can Patents Deter Innovation? The Anticommons in Biomedical Research*, 280 *SCI.* 698 (1998); Rebecca S. Eisenberg, *Patents and Data-Sharing in Public Science*, 15 *INDUS. & CORP. CHANGE* 1013 (2006); Robert Cook-Deegan & Tom Dedeurwaerdere, *The Science Commons in Life Science Research: Structure, Function and Value of Access to Genetic Diversity*, 58 *INT'L SOC. SCI. J.* 299 (1996).

Table 1: IP Practices: Software v. Biotechnology

	Software	Biotechnology
Predominant Form of IP protection	Copyright	Patent
Development Timeline	Short with high turnover	Long
Need for equipment/laboratory space	Low	High
Regulatory review and oversight	Low	High
Product Granularity	Low	High

The most significant difference is that the former is written in code and is thus generally protected by copyright, while the latter is generally characterized by empirical scientific work and concomitant insights and is thus subject to patent protection (with the exception of bioinformatics and related disciplines). The differences between copyright and patent are significant. Copyright attaches to work automatically (and is thus cheap to obtain) and prevents copying of written code or text.⁴⁵ A copyright in a work lasts for up to 70 years (depending on the jurisdiction) and there is little maintenance cost, though enforcement can be expensive.⁴⁶

Patents, in contrast, are granted to inventions that meet requisite subject matter conditions as well as standards of utility, non-obviousness, and novelty.⁴⁷ Patents are expensive to obtain and have significant maintenance costs (not to mention high enforcement costs). Patents essentially provide the patent holder with the right to exclude others from

45. 17 U.S.C. §§ 101–122 (2006).

46. 17 U.S.C. §§ 301–305 (2006).

47. 35 U.S.C. §§ 101–103 (2006).

practicing the invention.⁴⁸ The relationship between copyright and patents is something like the relationship between a cake recipe and the cake one can make. The copyright essentially prevents others from copying the recipe itself; the patent gives the holder the right to prevent others from making the cake for commercial distribution.

Software and biotechnology further differ in terms of the development time of products as a general principle. As a gross generalization, software can be developed rather quickly and generally has a short market turnover with improved versions and competitor products emerging quickly. There is no government approval requirement for such products and they can be placed on the market rapidly. In contrast, biomedical products—the end result of biotechnology research—require long development times and lengthy government regulatory review with ongoing oversight.⁴⁹ Additionally, the stereotypical software development process requires little more than computer technology and human innovators, while biotechnology generally requires expensive specialized equipment, laboratory space, and access to biological substrates and various research tools, all of which are subject to rigorous codes and audit by regulatory authorities.⁵⁰

A final difference exists in the need for product granularity. For software, there is no limitation on the nature and number of changes that can be made to the product as it is developed and even subsequent to market entry. In contrast, the significant regulatory requirements faced by biomedical products mean that a single product must be frozen at the stage of development in which it enters the regulatory process; any changes made thereafter could result in redoing earlier development stages and thus cause significant delays. This issue is discussed in more detail later.

Proponents of open source in biotechnology have taken the position that these differences are not limiting and that open source can be successfully applied in this area.⁵¹ Just as in

48. ROCHELLE COOPER DREYFUSS & ROBERTA ROSENTHAL KWALL, *INTELLECTUAL PROPERTY: TRADEMARK, COPYRIGHT AND PATENT LAW* 564 (2d ed. 2004).

49. *See infra* Part III.

50. *See infra* Part III.

51. *See* HOPE, *supra* note 9, at 189 (“ . . . I argue in this chapter and the next that none of the differences between software and biotechnology constitutes an insurmountable obstacle to implementing an open source

software, open source in biotechnology is not intended as a rejection of IP *per se*. Rather, the aim is to control IP to achieve the goal of maximum production of knowledge and to ensure that knowledge remains open and available even once modified.

As described by its proponents, open source in biotechnology starts with IP—in this case a patent or patents—on relevant material. The intent is that the patented material can then be licensed on open source terms: non-exclusively and (generally) royalty free. Often an open source license will also include a viral clause, analogous to the GPL or copyleft provision in open source software, that obligates licensees to share improvements or modifications on similar open source terms. The aim is to insert future controls in order to ensure that the open source objectives continue to be met.⁵² There can also be an obligation to “grant-back” to the licensor on open source terms, any improvements to the licensed technology.⁵³ For example, in the *CAMBIA BiOS License for Genetic Resources Indexing Technologies, Version 1.3* (BiOS GRIT), there is an obligation for licensees to share all “improvements” with BiOS to be further licensed on similarly open source terms.⁵⁴ The idea there is that the original licensor would become a repository of all knowledge relating to the originally licensed technology and would ensure that all such knowledge was then available to licensees—with the aim of maximum possible knowledge production.⁵⁵

‘biobazaar.’”).

52. In this sense, it is arguable that open source licensing is a form of defensive patenting.

53. See, e.g., The CAMBIA BiOS License for Genetic Resources Indexing Technologies (version 1.3), <http://www.bios.net/daisy/GRITLicense/750/1170.html> (last visited Oct. 27, 2009) [hereinafter BiOS GRIT]. In some ways, the obligation to grant back rights is in opposition to the philosophy of open source. However, as used here, the notion is to heighten knowledge sharing potential by ensure that licensors and licensees freely benefit from all knowledge related to the patented information.

54. *Id.* § 3.

55. Some, e.g., Janet Hope maintain that the CAMBIA BiOS license is not truly open source because of the control being in the hands of CAMBIA. See, e.g., Janet Hope, *Open source genetics: a conceptual framework in GENE PATENTS AND COLLABORATIVE LICENSING MODELS PATENT POOLS, CLEARINGHOUSES, OPEN SOURCE MODELS AND LIABILITY REGIMES* 191–92 (Geertrui Van Overwalle, ed., 2009); see also Dianne Nicol and Janet Hope, *Cooperative Strategies for Facilitating Use of Patented Inventions in*

Putting such licenses into practice has proven to be far from simple, especially for any license that aims to apply as open source licensed quantities are developed into commercial drug products. Key questions include: what happens to open source information once licensed? Can a licensee make improvements and then patent that information? Can a licensee patent innovations *derived from* open source material? Is there an obligation to share improvements with the licensor or other licensees? And fundamentally, what happens to open source licensed material as you move downstream to commercial products? Is there any incentive for participation in such a system? These questions for open source in the commercial drug development context are examined in greater details below.

C. OPEN SOURCE BIOTECHNOLOGY IN PRACTICE?

There are a few examples of groups attempting to put open source biotechnology into an applied context.⁵⁶ Possibly the most well known is the BiOS initiative of CAMBIA, an Australian nonprofit which is dedicated to making genomics resources widely available, particularly in the agricultural sector.⁵⁷ In essence, BIOS is intended to operate as a repository for patented information in a few fields, including, for example, “genetic resources indexing technologies.”⁵⁸ A party developing such a technology chooses to license the technology, molecule or substance to BiOS for purposes of making the technology accessible. BiOS then takes on the responsibility of licensing these materials on open source terms to all comers on certain terms, deemed by BiOS to promote openness and access.

The BiOS model has not been fully tested in a commercial context, however, and it is not clear whether it presents an acceptable alternative for developers of applied products. For example, among other things, the BiOS GRIT that is currently available states that the open source terms of that agreement override any other contract or license held and bars the licensee

Biotechnology,” 24 LAW IN CONTEXT 85, 107 (2006) (not disputing the accuracy of this comment, but rather pointing to the CAMBIA license as an illustration of an open source-like approach).

56. Janet Hope explores these examples as well as a number of others in *BioBazaar*. HOPE, *supra* note 9, at 309–18.

57. See BiOS Home Page, <http://www.bios.net/daisy/bios/home.html> (last visited Oct. 27, 2009).

58. *Id.*

from entering into contracts with conflicting terms.⁵⁹ Such a term may appear the most direct way of ensuring that open source terms survive subsequent contractual relationship. Conceptually, however, it has the potential to make ongoing development relationships very difficult for the BiOS licensee.

Other efforts are also underway, though for the most part these focus on drug discovery effort, which are relatively free from complex licensing arrangements. For example the Open Source Drug Discovery⁶⁰ (OSDD) organization, established recently in India, endeavors to establish an open source genomic community aimed at leveraging individual efforts in drug discovery for certain identified projects to increase access to outputs. Like BiOS, OSDD offers itself as a repository for material given by researchers who have an interest in advancing access to innovations and therefore agree to OSDD's terms in submitting their materials to it. Among other things, the OSDD license agreement obligates contributors to share their innovations with OSDD, as well as any improvements on that innovation.⁶¹ In informal conversations, OSDD has stated that it intends to use the materials in its database to advance drug discovery and development. However, as of yet, there is no indication as to how this would proceed.

The fundamental question of this article is whether an open source drug development pathway is a viable option. Toward that end, I first review in some detail the scientific and regulatory steps required in drug development. Thereafter, I evaluate the potential of open source in this process.

III. DRUG DEVELOPMENT

Drug development refers to the processes involved in taking a candidate drug or biologic⁶² through the stages

59. BiOS GRIT, *supra* note 53, § 3.4.

60. OSDD, *supra* note 17.

61. Open Source Drug Discovery TWiki Registration Terms and Conditions § 3.2 (Proprietary Rights), <http://sysborgtb.osdd.net/bin/view/TWiki/TWikiRegistration> (last visited Oct. 20, 2009).

62. U.S. statutory law distinguishes between a drug (“intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease.” 25 U.S.C. § 321 (2006)) and a biologic (“any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product or analogous product applicable . . . to the prevention, treatment or cure of disease.” 42

necessary to obtain marketing approval. The process begins with the pre-clinical studies required to show sufficient safety to enter into the clinical process of human testing. In general, the end goal of drug development is to have a product that is approved by relevant regulatory authorities and can be prescribed to or otherwise made available to patients.

Joseph A. DiMasi and his colleagues at Tufts University have demonstrated that the drug development process is lengthy and expensive.⁶³ There is much debate to just how expensive the process is: Merrell Goozner and Marcia Angell have attacked drug industry accounts that the cost of development for a drug is around \$800 million dollars, suggesting that this figure includes hefty—and perhaps unjustified—amounts for marketing and promotional budgets.⁶⁴ This high estimate reflects the fact that successful (or even unsuccessful) drug development, starting from an early stage of research and development, requires consideration and strategy on a wide range of factors including, *inter alia*:

-identification of the disease indication⁶⁵ to be treated,

U.S.C. § 262(i) (2006)—these definitions are intended to distinguish between small molecule products and large molecular entities produced in living cells. In the U.S., drugs and biologics are generally approved under distinct, though analogous, regulatory pathways and by different divisions of FDA (i.e. the Center for Drug Evaluation and Research (CDER) versus the Center for Biologics Evaluation and Research (CBER) (with some limited exceptions)). For purposes of this article, the term “drug” is used to include drugs and biologics.

63. See Joseph A. DiMasi et al., *The Price of Innovation: New Estimates of Drug Development Costs*, 22 J. HEALTH ECON. 151, 152 (2003).

64. MARCIA ANGELL, *THE TRUTH ABOUT THE DRUG COMPANIES: HOW THEY DECEIVE US AND WHAT TO DO ABOUT IT* (2004); MERRIL GOOZNER, *THE \$800 MILLION PILL: THE TRUTH BEHIND THE COST OF NEW DRUGS* (2004).

65. Drugs are approved for particular “indications,” which denote the conditions or diseases they are intended to treat; usually the “indication” for a drug is very narrow, so a drug will be approved not for the treatment of cancer, or even for cancer in a particular organ such as the bladder. Instead it will be approved for a certain type of bladder cancer, and often for a particular stage and sub-type of cancer and treatment priority such as a “second-line treatment for stage 3 superficial bladder cancer.” As far the drug regulatory authorities (Health Canada or FDA) are concerned, once approved for any particular indication, a drug may generally be used, on the judgment of the prescriber, for any condition whatsoever. That is, the health authorities do not regulate the practice of medicine; they are the gatekeepers for letting drugs into the market. Physicians are constrained in their use of drugs “off-label” by their own assessments of drug safety and efficacy, plus very important considerations of liability and reimbursement.

- potential for adverse events,
- intellectual property landscape,
- regulatory requirements and hurdles,
- the ability to conduct research and trials in a regulatory compliant manner,
- potential to manufacture and deliver the drug/compound,
- willingness of payors to pay for the end product, and
- the potential market for the product.

It is worth noting that the high figure includes opportunity costs as well as the costs of both successful and unsuccessful candidates, and not just those entities that come out of research and development and are successfully developed into commercial products. The latter is significant since even after years of preclinical study, 75-80% of drugs that begin clinical trials do not make it through to be approved products.⁶⁶

Many dispute the high estimates given for drug development costs,⁶⁷ arguing that pharmaceutical companies fold in marketing and other administrative costs in order to create the perception that high R&D costs justify high prices for end products.⁶⁸ For the present discussion, it is not material whether the cost is \$50 million or \$800 million per novel candidate; the point is that the process is, in absolute terms, expensive and the risks of failure are high. The various steps in the process are described below.

A. DEMONSTRATING SAFETY AND EFFICACY: PRE-CLINICAL AND CLINICAL TRIALS

Once a candidate is selected for development, the goal is to meet the regulatory requirements so that a marketing authorization will be granted. As a general rule regulators require a sponsor to demonstrate that a proposed drug (or

66. See, e.g., DiMasi et al., *supra* note 63, at 165 (“Our statistical analysis of compounds in the Tufts CSDD database of investigational drugs that met study criteria yielded a predicted final clinical success rate of 21.5%.”).

67. See, e.g., ANGELL, *supra* note 64; GOOZNER, *supra* note 64.

68. See, e.g., ANGELL, *supra* note 64. Christopher P. Adams & Van V. Brantner, *Estimating The Cost Of New Drug Development: Is It Really \$802 Million?*, 25 HEALTH AFF. 420 (2006) (stating that some variation in cost of development is due to the firm’s strategic choice).

biologic) is safe and efficacious and that the benefits of the drug (or biologic) outweigh the risks at the specified dose and for the specified indication.⁶⁹ These overarching standards, as well as the specific clinical trials required, are harmonized to a degree amongst international regulatory authorities including the Food and Drug Administration (FDA) in the U.S., the European Medicines Agency (EMA), and other worldwide bodies. In fact, these countries collectively participate in the International Conference on Harmonization (ICH) which directs its focus on making “recommendations on ways to achieve greater harmonization in the interpretation and application of technical guidelines and requirements for product registration in order to reduce or obviate the need to duplicate the testing carried out during the research and development of new medicines.”⁷⁰

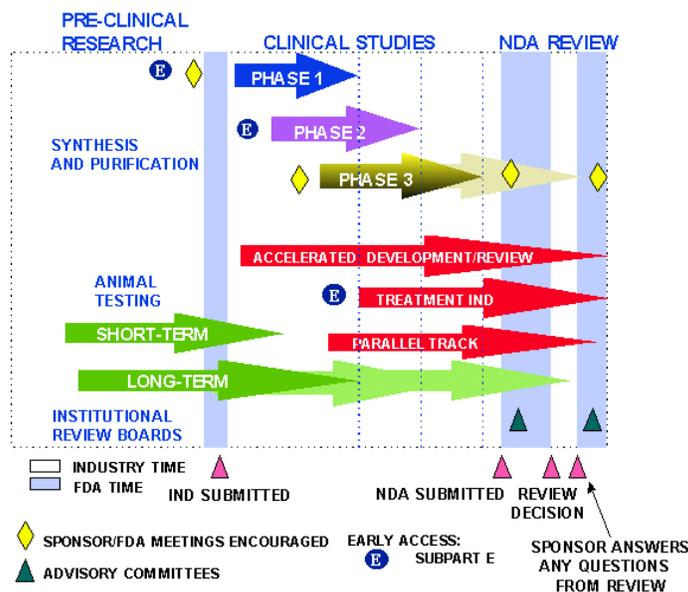
The following diagram, taken from the FDA website, gives an overview of the process as implemented in the U.S.⁷¹ The red arrows refer to variations on the approval route that may be used when there is an identified unmet medical need or there is pressure to allow the drug for use, even while it is being studied. These variations have specific requirements and are only applicable in limited situations.

69. 21 U.S.C. § 355(b) (2006).

70. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, <http://www.ich.org/cache/compo/276-254-1.html> (last visited Oct. 20, 2009) (“The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration.”) [hereinafter ICH]. This article discusses the FDA requirements while acknowledging that similar requirements exist for approval in Canada, the European Union, Japan, Australia, and a number of other developed countries.

71. CTR. FOR DRUG EVALUATION AND RESEARCH, FOOD AND DRUG ADMIN., THE CDER HANDBOOK 4 (1998), available at http://druganddevicelaw.net/CDER_handbook.pdf (CDER Handbook is currently under revision; non-revised version provided by source outside of FDA); see also Jim Beck & Mark Herrmann, *FDA’s CDER Handbook – Undergoing Revision*, DRUG AND DEVICE LAW (Aug. 14, 2009, 11:42AM), <http://druganddevicelaw.blogspot.com/2009/08/fdas-cder-handbook-undergoing-revision.html> [hereinafter CDER Handbook].

**Diagram 1: The New Drug Development Process:
Steps from Test Tube to New Drug Application Review**



Drug development generally begins after a target molecule, process, or pathway has been identified.⁷² As in the above chart, the first step in drug development is to conduct a barrage of standard pre-clinical studies on the identified molecule in an effort to provide baseline evidence that it is safe and efficacious; this work is a precursor to putting the molecule into human beings.⁷³

Preclinical testing is undertaken to evaluate the drug's toxic and pharmacologic effects through *in vitro* and *in vivo* laboratory animal testing.⁷⁴ As a part of this process,

72. See generally ULF MADSEN & TOMMY LILJEFORS, TEXTBOOK OF DRUG DESIGN AND DISCOVERY 1–34 (2002) (overviewing basic drug design and discovery).

73. 21 C.F.R. § 314.50 (2009).

74. CTR. FOR DRUG EVALUATION AND RESEARCH, FOOD AND DRUG ADMIN., GUIDANCE FOR INDUSTRY, INVESTIGATORS, AND REVIEWERS: EXPLORATORY IND STUDIES 2 (2006), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformat>

genotoxicity screening is performed. In addition, researchers undertake investigations on drug absorption and metabolism, the toxicity of the drug's metabolites, and the speed with which the drug and its metabolites are excreted from the body.⁷⁵ At the preclinical stage, the FDA will generally ask, at a minimum, that sponsors: (1) develop a pharmacological profile of the drug, (2) determine the acute toxicity of the drug in at least two species of animals, and (3) conduct short-term toxicity studies ranging from two weeks to three months, depending on the proposed duration of use of the substance in the proposed clinical studies.⁷⁶ All of this work must be done according to stringent Good Laboratory Practices (GLP), which require meticulous control and recording of every aspect of processes employed.⁷⁷ The GLP standards differ materially from controls and procedures that would be ordinarily practiced in a research institution. Thus, research carried out first in a university laboratory generally has to be repeated in GLP facilities to be acceptable for regulatory submissions. Many companies contract their preclinical work out to specialized companies that undertake these kinds of trials for a fee.

With sufficient preclinical data evidencing the safety of the molecule, sponsors can move forward toward undertaking clinical trials. In order to initiate this process and prior to being allowed to begin any trials in human beings, the sponsor will need to file an "Investigational New Drug" (IND) application or the equivalent.⁷⁸ The IND is aimed at demonstrating to regulators that the sponsor has satisfactorily conducted sufficient pre-clinical investigations to suggest that the drug will be safe and potentially effective in humans.⁷⁹ Generally, at

ion/Guidances/ucm078933.pdf [hereinafter FDA IND Guidance].

75. *Id.* at 11.

76. FDA, Small Business Assistance: Frequently Asked Questions on Drug Development and Investigational New Drug Applications, Investigational New Drug Application: What are the FDA Requirements for Pre-Clinical Studies?, <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/ucm069898.htm> (last visited Dec. 9, 2009).

77. *Id.*; see 21 C.F.R. § 58 (2009).

78. 21 C.F.R. § 312.1(a) (2009).

79. FDA, Investigational New Drug (IND) Application, <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm> (last visited Oct. 20, 2009) [hereinafter FDA IND Application website].

this stage the sponsor will meet with the regulator to discuss the information that is available or being developed about the molecule, process, or pathway and address questions that might be raised.

If there are no objections to the IND within a specified period (thirty days in the U.S.),⁸⁰ the sponsor will then initiate the procession of clinical trials. The trials are typically conducted, per regulatory directives, in four phases:

- Phase 1: The drug is tested in a few healthy volunteers (generally less than a hundred) to determine if it is acutely toxic and to obtain basic safety data, dosage, pharmacology data, etc.
- Phase 2: Various doses of the drug are tried in a small number of individuals with the targeted disease or condition to determine basic efficacy data and to collect additional safety data.
- Phase 3: The drug is typically tested in multiple comparative, double-blind controlled trials to demonstrate that the product is safe and effective for its intended use. Sponsors typically confer with the FDA prior to starting these Phase 3 trials to determine what data is needed, since these trials often involve hundreds of patients and are very expensive.
- Phase 4: These are post-approval trials that are sometimes a condition attached by the FDA to the approval.⁸¹

All trials must be conducted according to Good Clinical Practices (GCP), which are rules promulgated by regulators and designed to ensure that research is conducted in a transparent and reliable manner.⁸² The GCP obligations are

80. 21 C.F.R. § 312.40(c)(1) (2009).

81. Lewis J. Smith, *Types of Clinical Studies*, in *DRUG AND BIOLOGICAL DEVELOPMENT: FROM MOLECULE TO PRODUCT AND BEYOND* 107, 107–22 (Ronald P. Evens ed., 2007).

82. See 21 C.F.R. §§ 50, 56 (2009). The International Committee on Harmonisation defines Good Clinical Practice as a “standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.” ICH, ICH HARMONIZED TRIPARTITE GUIDANCE:

significant and pose an additional hurdle to organizations involved in this process. GCPs require attention to a range of factors including informed consent, record-keeping, design of trials, safety assessments, trial monitoring, financing, and other relevant considerations.⁸³ Furthermore, everything done under GCP is subject to audit.⁸⁴

It is important to recognize that carrying out clinical trials requires significant and varied expertise at each new stage. Phase 1 trials (also known as “first in human”) trials are “[i]nitial studies to determine the metabolism and pharmacologic actions of drugs in humans, the side effects associated with increasing doses, and to gain early evidence of effectiveness.”⁸⁵ They “may include healthy participants and/or patients,”⁸⁶ and often must be carried out in special units that have the capacity to monitor and respond to dosing responses very quickly.⁸⁷ Phase 2 trials primarily assess relevant dosing but also offer first indications of efficacy as well as additional safety data.⁸⁸ Phase 3—or pivotal trials—are expanded trials undertaken after the preliminary evidence suggests that drug effectiveness has been obtained.⁸⁹ These much larger and more expensive trials gather additional information to evaluate the

GUIDELINE FOR GOOD CLINICAL PRACTICE E6(R1) § 1.24 (1996) <http://www.ich.org/> (click “E” under the ICH logo; then click “Good Clinical Practice” hyperlink; then click “E6(R1)” link) (last visited Oct. 20, 2009) [hereinafter ICH Guidance]. The ICH Guideline has been adopted by the FDA. ICH, GUIDANCE FOR INDUSTRY: E6 GOOD CLINICAL PRACTICE: CONSOLIDATED GUIDANCE GUIDELINE FOR GOOD CLINICAL PRACTICE (1996), *available at* <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129515.pdf> (the ICH Consolidated Guidance has been adopted by the FDA as a condensed version of the ICH Guidance) [hereinafter ICH Consolidated Guidance]. The FDA and the EMEA recently announced that they were undertaking a joint eighteen-month focus study on GCPs designed to ensure that clinical trials submitted in drug marketing applications in the United States and Europe are conducted uniformly, appropriately, and ethically. *See* Press Release, Food and Drug Admin., FDA, European Medicines Agency Launch Good Clinical Practices Initiative (Aug. 3, 2009), <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm174983.htm> (last visited Oct. 20, 2009).

83. *See, e.g.*, ICH Guidance, *supra* note 82, at §§ 4–6.

84. *Id.*

85. ClinicalTrials.gov, Glossary of Clinical Trials Terms, <http://www.clinicaltrials.gov/ct2/info/glossary> (last visited Oct. 20, 2009).

86. *Id.*

87. Smith, *supra* note 81, at 108.

88. ClinicalTrials.gov, *supra* note 85.

89. *Id.*; *see* Smith, *supra* note 81, at 109.

overall benefit-risk relationship of the drug and to provide an adequate basis for approval and labeling.⁹⁰

The number of participants, duration of trials, study design, dosing, and many other parameters must be chosen for each trial in accordance with the specific characteristics of the drug, including identified potential for toxicity, potential reactions with other drugs, absorption, metabolism and excretion characteristics, as well as the mechanics of dosing and potential patient adherence.⁹¹ Many of these considerations are outlined in therapeutic area-specific guidance documents authored by the FDA in the U.S.,⁹² and analogous bodies in other jurisdictions.

All along this process, sponsors will confer with regulatory authorities to identify unexpected results, adverse events, potential changes to the protocol, and any other unforeseen or significant events.⁹³ It is additionally important to note that once the clinical trial process begins, the sponsor becomes increasingly bound to the specific compound and formulation being tested. Any changes to the compound itself or the manufacturing process need to be reported to regulators and could, hypothetically, invalidate study results generated with a prior or alternate version of the compound.⁹⁴

Once the entire package is completed, the sponsor will submit a New Drug Application (NDA)⁹⁵ or Biologics License

90. ClinicalTrials.gov, *supra* note 85.

91. CTR. FOR DRUG EVALUATION AND RESEARCH & CTR. FOR BIOLOGICS EVALUATION AND RESEARCH, FOOD AND DRUG ADMIN., GUIDANCE FOR INDUSTRY PROVIDING CLINICAL EVIDENCE OF EFFECTIVENESS FOR HUMAN DRUG AND BIOLOGICAL PRODUCTS (May 1998), <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM078749.pdf> [hereinafter FDA Drug Efficacy Guidance].

92. See, e.g., FDA, Clinical/Medical Drug Guidances, <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064981.htm> (last visited Oct. 21, 2009).

93. FDA, The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective, <http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143534.htm> (last visited Oct. 20, 2009) [hereinafter FDA Drug Review Process website].

94. Prabu Nambiar & Steven R. Koepke, *CMC Sections of Regulatory Filings and CMC Regulatory Compliance During Investigational and Postapproval Stages*, in FDA REGULATORY AFFAIRS: A GUIDE FOR PRESCRIPTION DRUGS, MEDICAL DEVICES AND BIOLOGICS 203-06 (Douglas J. Pisano & David Mantus eds., 2008).

95. FDA, New Drug Application (NDA),

Application (BLA)⁹⁶ (or equivalent in other jurisdictions) to the FDA. The review time and process varies from country to country, but will generally involve questions to the sponsor during the review and may potentially involve the convening of an advisory board of experts in the field to advise the regulator on how to respond. In the U.S., review timeframes range from six months for fast track review to ten-plus months for non fast-track applications.⁹⁷

There is no guarantee of approval, even if the regulator has been involved throughout the development process. The application is generally reviewed by multiple disciplines separately, including pharmacology, toxicology, CMC (chemistry, manufacturing, controls), and medical.⁹⁸ Any of these groups may find issues that they feel make the risk-benefit balance unacceptable. In recent years, the number of

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/NewDrugApplicationNDA/> (last visited Oct. 21, 2009).

96. The Biologics License Application (BLA) is a request for permission to introduce, or deliver for introduction, a *biologic* product onto the market. See 21 C.F.R. § 601.2 (2001). The BLA is regulated under 21 C.F.R §§ 600–680. In many ways, the BLA is analogous to the NDA, though the specific requirements reflect manufacturing, safety, and efficacy issues that are unique to biologics. FDA, Biologics License Applications (BLA) Process (CBER),

<http://www.fda.gov/BiologicsBloodVaccines/DevelopmentApprovalProcess/BiologicsLicenseApplicationsBLAProcess/default.htm> (last visited Oct. 21, 2009) [hereinafter BLA Process].

97. In the U.S., the Prescription Drug User Fee Amendments (“PDUFA”) II (as well as subsequent PDUFA re-authorizations in 2002 and 2007) call for the FDA to review and act on 90 percent of priority NDAs and BLAs within six months and standard NDAs and BLAs and efficacy supplements within ten months. Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105–115, § 112, 111 Stat. 2296 (1997) (establishing a priority review pathway); 21 U.S.C. § 379g(l) (2009) (establishing prescription drug user fees in order fund prescription drug review by FDA); FDA, Section A: PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 Through 2012, <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm119243.htm> (visited January 17, 2010).

98. Ramzi Dagher, Deputy Div. Dir., Office of Oncology Drug Prods. (ODDP), Center for Drug Evaluation and Research (CDER), Food and Drug Admin., The CDER Review Process, (Apr. 16, 2007). It is worth noting that health authorities that “approve” drugs make their determinations on the basis of scientific criteria of safety and efficacy; they do not take into consideration the costs. Costs are generally a concern for other administrative bodies—like the Centers for Medicare and Medicaid Services (CMMS) in the U.S.

new drugs representing new chemical entities (NCE), as opposed to “follow-on” or “me-too” versions of previously existing drugs, approved by the FDA in the U.S. has declined sharply. In 2008, there were under twenty-five such NCEs approved by the FDA in the U.S.⁹⁹ Moreover, in the wake of Vioxx and other highly publicized safety issues, regulators have implemented numerous additional controls—pre-approval and post-approval—that may further limit the availability and approval of new drugs.¹⁰⁰

Even after approval, there are continuing monitoring activities. As a condition of approval, regulators may require post-marketing studies (Phase IV) to track adverse events or safety issues of concern.¹⁰¹ Sponsors are required to track and report adverse events and to continually monitor and update labels as new information is made available about the safety of the drug.¹⁰² Further, before entering the market, the sponsor will need to interact with pricing and reimbursement administrators in multiple countries to determine the actual availability of the drug to patients.¹⁰³ Depending on the sponsor’s aims, post-marketing will also require attention to IP and regulatory exclusivities to ensure that monopoly rights are not being infringed. This in itself can be a labor intensive and costly undertaking.

99. PhRMA, New Medicines Approved in 2008, <http://www.phrma.org/files/2008Approvals.pdf> (last visited Oct. 20, 2009).

100. Bette Hileman, *FDA Moves to Improve System*, CHEMICAL & ENGINEERING NEWS, Nov. 29, 2004 at 16-17, available at <http://pubs.acs.org/cen/news/8247/8247earlygov.html>; see Press Release, Food and Drug Admin., FDA, Public Health Advisory: Safety of Vioxx (May 22, 2009), <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm106274.htm> (discussing Merck’s decision to withdraw Vioxx and the FDA’s cooperation therewith).

101. Smith, *supra* note 81, at 111. Note as well that the FDA Amendments Act of 2007 (FDAAA), Pub. L. No. 110–85, 121 Stat. 823 (2007), added Risk Evaluation and Mitigation Strategy (REMS) provisions which the FDA can impose on drugs associated with greater safety risks; see 21 U.S.C. § 355-1 (2009). These additional obligations, which can include additional distribution controls or monitoring efforts, can be very expensive.

102. *Id.*

103. See Stephen F. Carroll, *Discovery and Nonclinical Development*, in DRUG AND BIOLOGICAL DEVELOPMENT: FROM MOLECULE TO PRODUCT AND BEYOND 84-107 (Ronald P. Evens ed., 2007).

B. GENERICS

The generic pathway offers an abbreviated route for completing the regulatory requirements discussed above and, as such, is cheaper, less risky, and less burdensome to complete.¹⁰⁴ It is important to realize, however, that approval of a generic version of a drug is *not* automatic once there is an approved brand version of a drug. First, generic approval is only available once relevant patent terms and exclusivities have expired, so there is generally some period before an application for approval of a generic can be submitted.¹⁰⁵ Second, the FDA must individually approve generic versions of drugs based on GLP, GCP, and GMP (Good Manufacturing Practices) compliant evidence of bioequivalence and bioavailability,¹⁰⁶ as well as support for any differences between the proposed generic version and the approved drug.¹⁰⁷ For the clinical trial data related to the drug, the generic applicant can rely on the brand drug's original submission.¹⁰⁸ Thus, generics get a "shortcut" to marketing authorization and avoid the most failure prone aspect of drug development.

Nonetheless, generics are subject to the same regulatory parameters as their brand counterparts. Generic manufacturers also have post-marketing safety reporting obligations and are subject to similarly tight controls on

104. This discussion has merged drugs and biologics in the discussion of drug development. Importantly however, for purposes of generics, there are very different regulatory approval mechanisms because of the nature of the substances themselves. It is much more straightforward to copy small molecule drugs based on chemical formulae and conformation information. Biologics, by their nature, are very large complex molecules and are produced in cells rather than being synthesized. As a result, very minor variations in production conditions can have drastic impacts on safety and efficacy. While there is no generic pathway for biologics in the U.S. as of the writing of this article, this may change with the passage of a health care bill by Congress in 2010.

105. *See generally* 21 U.S.C. § 355(j) (2006); 21 C.F.R. §§ 314.53, 314.92, 314.94, 314.95 (2009) (detailing the general procedure for submitting abbreviated applications).

106. *See e.g.*, FDA, Pharmaceutical cGMPS for the 21st Century – A Risk-Based Approach: Second Progress Report and Implementation Plan, http://www.fda.gov/cder/gmp/gmp2004/GMP_Finalreport2004.htm (last visited Oct. 22, 2009) (discussing FDA initiative focused at increasing drug product quality through regulation).

107. 21 C.F.R. § 314.94 (2009).

108. *Id.*

ingredient quality, sourcing, and other manufacturing issues.¹⁰⁹ The net result is that while it is less burdensome to obtain regulatory approval of a generic drug, it is still a costly process with strict controls and follow up that must be maintained. Generics cannot simply appear on the market; they too must be the subject of careful preparation and planning by the sponsoring entity.

C. PATENT TERMS AND EXCLUSIVITIES

It is worth noting the basis for drug market exclusivities. These remain key drivers for conventional drug development because pharmaceutical companies are able to earn a significant return on investment during these exclusivity periods. As explored in the next section, open source drug development changes this equation and thus may reset the incentive considerations.

In essence, there are two types of exclusivity: (1) that conferred by patent and (2) that conferred by regulators—also known as regulatory exclusivity (e.g. orphan drug) or data exclusivity (e.g., new chemical entity).¹¹⁰ Patent exclusivity reflects the IP landscape of the drug.¹¹¹ For the term of the relevant patent(s) on a drug, competitors are precluded from using that protected information. Generally, when a drug is approved, it or the processes used in its manufacture are covered by a host of patents, the strongest of which may be a “composition of matter” patent that protects the molecule representing the active ingredient in the drug.¹¹² As long as a molecule is under patent protection, no one can market a copy of the drug without infringing the patent (or being obligated to license the IP). Critics often point to patents and the aggressive enforcement of patent rights by pharmaceutical companies as a leading cause of high drug prices.¹¹³

Data exclusivity deserves special mention. Data exclusivities conferred under national regulatory regimes may add market protection, and for that reason are highly pursued

109. 21 C.F.R. §§ 314.96, 314.98 (2009).

110. 21 U.S.C. §§ 351(j)(5)(D)(iii)-(iv), 355(j)(5)(D)(iii)-(iv) (2006); 21 C.F.R. 314.108 (2009).

111. 35 U.S.C. § 156 (2000).

112. 35 U.S.C. § 101.

113. Nolan-Stevaux, *supra* note 12, at 274–76.

by most pharmaceutical companies. The original intent of data exclusivity provisions was to offer an additional incentive for drug development to pharmaceutical companies in exchange for a planned entry of generic versions of drugs.¹¹⁴ Data exclusivity effectively bars regulators from allowing any other drug application from relying on the data submitted and, in this sense, blocks *any* abbreviated submissions during the term of the exclusivity.¹¹⁵ Thus, during the term of exclusivity, no competitor can rely on the data for a brand name drug to obtain approval for a generic or copy of that drug. Hence, the generic pathway is not available and approval can only be based on submission of a full regulatory package. The two most common forms of data exclusivity in the U.S. are five years granted for “new chemical entities” that have never before been the subject of an FDA approval, and three years for a new indication that requires significant additional clinical studies.¹¹⁶

These data exclusivities generally run concurrently, though can extend beyond patent terms and are awarded for successful approval of new chemical entities or new indications for which significant clinical studies were required. Often times, pharmaceutical companies submit data for new indications to get the three-year exclusivity period at a time when their patent on a drug is close to expiration.¹¹⁷ The added regulatory exclusivity effectively prolongs the period of market exclusivity and is often referred to by critics as “evergreening.”¹¹⁸

114. Abbreviated New Drug Application Regulations, 54 Fed. Reg. 28,872, 28,896 (July 10, 1989); *see also* Frederick Tong, Note, *Widening the Bottleneck of Pharmaceutical Patent Exclusivity*, 24 WHITTIER L. REV. 775 (2002) (explaining that the original intent of the Hatch-Waxman legislation was to increase access to generic drugs).

115. During the term of data exclusivity, another party could submit an application for the same drug (provided that patent issues are addressed), but would have to submit a full New Drug Application because it could not rely on any data previously submitted. When there is no data exclusivity, and patents are addressed, the Abbreviated New Drug Application submission relies extensively on data on file at the agency. Abbreviated New Drug Application Regulations, 54 Fed. Reg. at 28,896.

116. 21 C.F.R. § 314.108 (2009).

117. Rebecca S. Eisenberg, *The Problem of New Uses*, 5 YALE J. HEALTH POL'Y L. & ETHICS 717, 727 (2005).

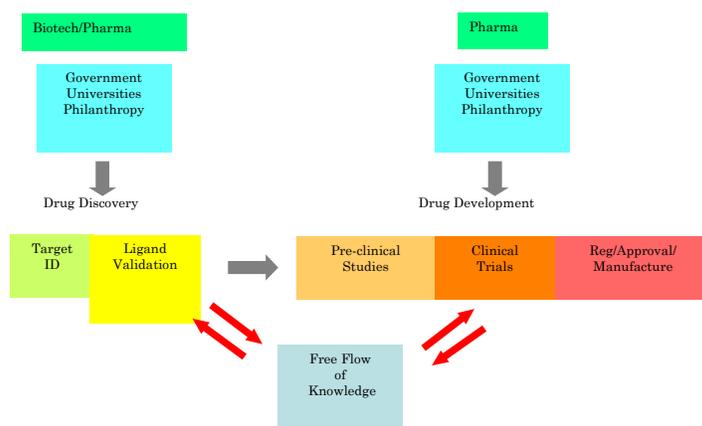
118. Robert Weissman, *Victory and Betrayal: The Evergreen Patent System of Pharmaceutical Company Tactics to Expand Patent Protections*, 23 MULTINATIONAL MONITOR, June 2002, <http://www.multinationalmonitor.org/mm2002/062002/weissman.html> (last

IV. OPEN SOURCE DRUG DEVELOPMENT

The regulatory requirements associated with drug development are significant and exist without respect to the IP context in which the development takes place. Thus, any compound licensed under open source terms is still subject to exactly the same regulatory requirements for market authorization, with some minor requirements that could differ under specific circumstances.¹¹⁹ Open source drug development *does* differ from conventional drug development in other ways, however.

The diagram below provides a rough outline of these differences.

Diagram 2: Open Source Drug Development¹²⁰



The blocks on the right side of the diagram, under the Drug Development heading, apply to any drug development, whether conducted using open source or any other IP approach.

visited Dec. 9, 2009).

119. There are limited ways that the IP status of a drug development project impacts regulatory obligations. For example, if there are no patents covering an approved drug, there will be no obligation to list patents in the so-called “Orange Book.” As such, any generic seeking to copy that drug would not have to file patent certifications as required under 21 C.F.R. § 314.94(a)(12)(ii) (2009).

120. Rebecca Goulding (2009) (diagram on file with author).

The key difference illustrated in the diagram between conventional drug development and open source drug development is that during the drug development process, there may be an ongoing flow of information to the public under an open source license. As shown above, open source licensing allows for ongoing sharing of information to the licensor and potentially to further licensees. With respect to drug development, this characteristic affects not only future or follow-on IP licensing, it also has likely impacts in terms of the management and financing of the long term development program. Each of these issues is explored further below.

As noted above, there are two interrelated rationales variously offered for undertaking open source drug development. One is that open source drug development is also a means of *promoting* the free flow of patented information, which will result in greater research freedom and more innovation overall.¹²¹ The idea is that open source licensing allows for a path to commercialization while keeping information broadly available. As such, it is argued more information will be available to others and innovation overall can flourish.¹²²

The other presumed goal of open source drug development is that it will yield less expensive, and hence make drugs, more

121. HOPE, *supra* note 9, at 105. There are also scientific organizations committed to this principle. For example, the BioBricks Foundation states as one of its goals, “to develop and provide educational and scientific materials to allow the public to use and improve existing BioBrick™ standard biological parts, and contribute new BioBrick™ standard biological parts.” See, e.g., The BioBricks Foundation, Our Goals, http://bbf.openwetware.org/Our_Goals.html (last visited Oct. 22, 2009) (discussing goals of the foundation).

122. See Rebecca S. Eisenberg, *The Shifting Functional Balance of Patents and Drug Regulation*, HEALTH AFF., Sept.–Oct. 2001, at 119–35 for this argument made outside of the open source context but in the drug context. She maintains that more sharing of information, including failed studies would allow for more innovation and better drug development overall. *Id.* The Food and Drug Administration Amendment Act (FDAAA), § 801 (2007), legislates a certain degree of sharing by requiring sponsors to post certain information about clinical trial undertaken and clinical trial results on the public clinicaltrials.gov website. It is arguable that this information is useful to researchers and clinicians alike. Nonetheless, posting clinical trial results does not *per se* facilitate the scope of sharing envisaged in open source licensing. As discussed throughout this article, an open source license would allow researchers access to *use* and *modify* any aspect of a patented compound. In contrast, the clinicaltrials.gov disclosure has no impact on the IP status of a compound.

accessible.¹²³ This line of thinking holds that if drug compounds are not patented and licensed with the intent of creating market monopolies, (1) it will be cheaper to license the relevant compounds for development, thereby reducing approval costs at the outset and reducing potential costs of the end product; and (2) there will be more parties making the drugs, more competition and, as a result, cheaper drugs. Inherent in this approach is an expectation or hope that generic manufacturers will readily enter the market if IP does not create a barrier and that the entry of the generic manufacturers will ensure that lower cost copies of a drug are available, with the net result of increasing accessibility overall.¹²⁴

Ultimately, this section attempts to answer critical questions about how an open source drug development effort would play out. This discussion considers: (1) how the OS status of an in-licensed compound would unfold and whether such a compound could realistically result in a drug that is, or whose components are, available on open source terms; (2) how an open source drug development effort could be organized given likely cost limitations on the effort; and (3) how such an effort would be financed in the likely absence of deep investments by pharmaceutical companies expecting exclusive rights to the final drug product. Although this article suggests that the challenges to open source drug development are significant, there are potential contexts in which it makes sense to pursue open source further. Moreover, it may be important to reconsider open source drug development in the context of novel financing models. It is possible that if incentives to initiate open source drug development were robust under these models, at least some of the aforementioned obstacles could be overcome.¹²⁵

A. INTELLECTUAL PROPERTY CONSIDERATIONS

To begin to understand how open source licenses impact drug development, this article assumes that the “key” (e.g. composition of matter) patent underlying a drug is open source licensed and that this open source license subjects the entire

123. Nolan-Stevaux, *supra* note 12, at 310–16.

124. HOPE, *supra* note 9, at 285–87.

125. This is a subject that merits more discussion and research in the future.

finished drug to the terms of the open source license.¹²⁶ That is, given the type of open source licensing described above (i.e. non-exclusive, royalty-free, available to all comers), all the elements of the final drug product would similarly be available for licensing on a non-exclusive, royalty-free basis, and for this reason it would be straightforward for a generic or other follow-on version of the drug to be manufactured.¹²⁷

If the drug relied on this single open source licensed patent, there would be no IP costs involved in in-licensing the patent related to drug development. In that case, the terms of the open source license on this in-licensed compound would apply to the final product as well. Ultimately, competitors or generic developers could license either the same in-licensed compound *or* the finished drug product royalty-free to make competing products.

At the same time, it is important to be aware that IP related to drug development generally requires more than one patented component. Thus, even if the active pharmaceutical ingredient compound is licensed or available on open source terms, it is possible that the finished drug itself could be treated in a conventional proprietary manner. For example, if the open source license on the drug compound allowed improvements on the compound to be patented and conventionally licensed, a drug developer could have an avenue for moving a drug that is developed from open source-licensed material into a conventional IP stream. Assume that a compound X is licensed on open source terms to company PHARMA. PHARMA does additional research on X and discovers that it is potentially more effective in treatment if ESP is added to it. It thus creates the improved version of X, namely X-ESP. The open source license terms, under which X was licensed, allow improvements to be separately patented and do not obligate the patenting party to carry on with open source license terms. PHARMA would then have effectively removed itself from any open source obligations with regard to

126. This commentary would also apply if the drug development sponsor owns the composition of matter patent and intends for the final drug product to be licensed on OS terms. If there were no other licenses necessary for development of the drug, the final product would be available for licensing on whatever OS terms set by the sponsor. That said, if multiple patents/licenses were necessary for development, the sponsor would still face issues with the interaction of OS and non-OS licenses as described in this subsection.

127. See discussion *infra* Part V.

X-ESP (of course, any developer of unimproved X would still be under the open source license obligations). PHARMA could then choose to proceed with drug development, with the possibility of a patent on the end product.

It is also important to recognize that the relationship between patents and drug development may be complex, and that this complexity may stand in the way of realizing an open source-licensed drug product. In reality, drugs do not usually rely on a single patented compound or single license, but instead generally depend on several—and potentially many—patents including composition of matter, delivery systems, use, manufacturing aspects, and others.¹²⁸ A conventional (non-open source) license for a patent generally requires the licensee to ensure that there is no infringement of the licensed patent when that licensed patent is combined with other IP.¹²⁹ Further, there are often other terms that dictate the conditions under which the licensed patent can be sublicensed—or whether it can at all.¹³⁰ Importantly, the conventional license generally may be revoked if you attempt to make the licensed patent information available non-exclusively or on terms that are not deemed to be protective enough.¹³¹

Such terms could have implications on the cost and

128. See *Generic Pharmaceuticals: Marketplace Access and Consumer Issues Before the S. Comm. on Commerce, Science, and Transportation*, 107th Cong. 58 (2002) (statement of Kathleen Jaeger, President and CEO of the Generic Pharmaceutical Association) (“[S]ince the enactment of Hatch-Waxman in 1984, the average number of patents filed per blockbuster has increased five-fold—from two to an astounding ten patents per drug.”), available at <http://www.gphaonline.org/resources/2002/04/22/drug-pricing-and-consumer-costs>.

129. See Eileen Smith Ewing, *Research and Development Collaborations*, in *BIOTECHNOLOGY AND THE LAW* 445, 461 (Hugh B. Wellons et al. eds., 2007).

130. See generally *id.* at 460–62 (explaining the license process).

131. *But see* BIOS GRIT, *supra* note 53, at § 3.4 (demonstrating that some developers of OS licenses attempt to address this potential by including terms in those OS licenses that would override conflicting terms in other licensed technologies or—alternatively—would invalidate the original OS license. “In the event that BIOS LICENSEE has pre-existing obligations to third parties, which obligations would conflict with BIOS LICENSEE’s obligations as defined in this Agreement, BIOS LICENSEE shall not make any use of the IP & Technology that would invoke such conflicting obligations, unless a waiver of said conflicting obligations is obtained by BIOS LICENSEE from said third party. . . . In the event that BIOS LICENSEE enters into an agreement the terms of which would conflict with BIOS LICENSEE’s obligations under this Agreement, the terms of this Agreement will prevail.”).

accessibility of IP information for the final product, particularly if there are multiple patents licensed for the production of a drug and not all of those patents are on open source terms. In that case, it would require a diligent effort to ensure that the open source license terms can be applied to the final product, without violating the terms of any conventional licenses. Drug developers could well be faced with the question of whether a non- open source licensed entity *plus* an open source licensed entity can *equal* an open source product, or whether the non-open source licensing provisions require that any product combining multiple patents respect the non-open source license terms. These are important questions and would determine whether an open source-licensed compound, when added to other necessary licensed information, would result in a product that could be open source-licensed or whose components would be licensable by others on similar non-exclusive, royalty-free terms.

B. COST AND ORGANIZATIONAL ISSUES

Putting aside the complexity of the IP inputs, the analysis turns now to the cost and organizational requirements of drug development. Conventionally, drugs are developed in, or under the auspices of a pharmaceutical company that invests significant resources and organizes the process for such a project in the expectation that market exclusivity will allow for some return on investment.¹³² In contrast, the financial incentives for a pharmaceutical sponsor to invest money and resources in open source drug development are limited; there the goal is for the final product (or all relevant IP inputs) to be available on open source licensed terms, meaning there would likely not, subject to the discussion in Section V *infra*, be an exclusive interest in the final drug product. One result of this different potential return is that it is likely that the sponsor of an open source drug would want to minimize the costs of development. Further, to the extent that open source drug development is intended to result in less costly, more accessible drugs, there is an additional impetus to make the development process less expensive.

In the software sector, the bazaar model of production has

132. See, e.g., Covance: the CRO for Drug Development Services, <http://www.covance.com/> (last visited Oct. 22, 2009) (example of third party vendor or Contract Research Organization).

been identified as the source, not only of creativity, but also of a lower cost, less hierarchical mode of production.¹³³ In that idealized model, individuals contribute their efforts from multiple decentralized nodes, minimizing space and equipment costs otherwise incurred by large hierarchical organizations.¹³⁴ Further, in the bazaar model there is no organizational lead, a further cost savings, and instead progress is made via the cumulative, potentially more creative, efforts of the participants.¹³⁵

Some have proposed that an analogous approach might be used in the drug development arena to similarly minimize costs and maximize participation.¹³⁶ Unfortunately, the potential for implementing such a model in drug development is limited by the very different requirements of that sector. Unlike most software development, drug development is characterized by significant regulatory requirements that dictate that work be carried out in laboratories expressly designed for such efforts. As described above, any clinical trials relevant to submission of a NDA or BLA must be carried out according to strict, regulatory-agency defined GCPs. Further, any preclinical work is subject to Good Laboratory Practices (GLP) while production of final products must conform with Good Manufacturing Practices (GMP). Altogether, these GXP—as they are sometimes known—mean that any work done on drug

133. See RAYMOND, *supra* note 37, at 27–78 (contrasting the bazaar, or open source, method of software development with traditional forms, and extolling the virtues of open source).

134. See HOPE, *supra* note 9, at 20 (“Open source development shows how groups of volunteers can ‘collaborate on a complex economic project, sustain that collaboration over time, and build something that they give away freely’—technology that can ‘beat some of the largest and richest business enterprises in the world at their own game.’”); see also OSDD, *supra* note 17 (noting that incipient efforts in OS drug discovery by the Open Source Drug Discovery Foundation rely heavily on this model for leveraging creativity while minimizing costs).

135. See generally RAYMOND, *supra* note 37 (summarizing the emergence of the OS movement in software and information technology).

136. See, e.g., Maurer et al., *supra* note 4, at 184 (arguing that well-designed open-source licenses are the key to containing Virtual Pharmas’ R&D costs.); HOPE, *supra* note 9, at 20 (“A key premise of this book is that open source principles of technology, development, licensing, and commercial exploitation offer at least a partial solution to the innovation lock-down caused by extensive public control over scientific and technological information within a highly concentrated industry structure.”).

development must be carried out in appropriate facilities, by individuals with the skills necessary to meet these requirements, and with the proper record-keeping and documentation undertaken.¹³⁷ As a general rule, these standards are not the norm in research laboratories and any work carried out in non-conforming manner would likely need to be redone for regulators to accept them.¹³⁸

Further, drug development has fixed phases and targets that must be met, generally in a sequential manner. The FDA meets with sponsors throughout the process to determine whether such targets—beginning with preclinical studies and continuing with the clinical trials themselves—have been achieved.¹³⁹ This process does not lend itself to a decentralized bazaar-like development process where multiple parties work toward the success of an end product. Instead, the drug development process likely proceeds best when there is a project manager ensuring that each stage and target has been appropriately met, and subject matter experts can guide specific elements of the process. These individuals may include project managers, experts in pre-clinical and clinical studies as well as individuals knowledgeable in the regulatory process, IP, financing, marketing and post-marketing issues.

Certain “virtual pharma” companies have found a way to embrace a decentralized organizational structure while maintaining the process controls necessary to meet drug development requirements.¹⁴⁰ The concept of “virtual pharma” is that all the functions of a large pharmaceutical company can be harnessed without the massive corporate structure that those entities generally have.¹⁴¹ Instead, in “virtual pharma,” a small number of experts work together to manage the process of drug development, and hire or commission the necessary experts in various functions as the process unfolds.¹⁴² Thus, the

137. See 21 C.F.R. pts. 210, 211 (2008) (GMPs); 21 C.F.R. pts. 50, 54, 56, 312 (2009) (GCPs); 21 C.F.R. pt. 58 (2009) (GLPs) (collectively, “GXP”).

138. For example, even work carried out outside the U.S. for submission in a U.S. NDA must have been carried out in compliance with regulations.

139. FDA Drug Review Process website, *supra* note 93.

140. See Hal Broderson, *Virtual Reality: The Promise and Pitfalls of Going Virtual*, 23 NATURE 1205, 1206 (2005) (“The virtual model gives management the flexibility to tap a vast network of clinical development talent—without actually bringing them in house.”).

141. *Id.*

142. *Id.*

“virtual” company may be composed only of an executive decision-maker, project manager, finance management, medical management, scientists who know the molecule and its biology, patent counsel and, depending on the context, one or two others. This team would be responsible for managing the process so that, for example, the many various necessary functions—such as appropriate toxicologists—might be brought on board as consultants during the appropriate phase of the project and so on. The benefit is that the company can operate in a lean—and potentially cost—saving—manner, but can still ensure that all necessary functions are represented.

Ultimately, sponsors are unlikely able to achieve the milestones and requirements of drug development in a bazaar-like model. A virtual pharma approach, however, may help minimize organizational and process related costs of drug development, especially in the earlier stages, while still ensuring that any work done will meet the standards of regulatory compliance required in the industry.

C. SUSTAINABLE FUNDING

Even if costs could be somewhat managed through a virtual pharma model, the extensive regulatory process means that drug development costs will still be significant and a large source of financing needs to be available. As noted, drug development currently rests on the expectation that market exclusivity will allow some return on investment. Pharmaceutical companies employ sophisticated risk analyses to gauge the likelihood of success and the potential returns that can be generated. Based on these analyses, the companies invest the millions of dollars that are required to harness the expertise, provide GXP compliant facilities, undertake the clinical trials, and put together a viable package for regulatory review in multiple countries.¹⁴³

Without the potential market returns permitted by exclusive market rights, it is possible that funding of the development process would need to come from sources other than pharmaceutical companies. The question then becomes: who would offer similarly sustainable funding and why?

143. See generally DiMasi et al., *supra* note 63 (providing a statistical analysis of the costs that go into drug development at various stages).

The answer to this question is well beyond the scope of this article. However, it is worth noting a few of the proposals that have been put forward on this issue. For example, currently, governments effectively pay for much of pharmaceutical development by expending large amounts to purchase pharmaceuticals at the end of the development process.¹⁴⁴ Some argue that governments could get a better return on their spending in this area by funding the upfront research into pharmaceuticals, thereby gaining access to non-proprietary, *cheaper*-end products.¹⁴⁵ While there is some logical appeal to this argument, it may be difficult for governments to risk taxpayer money on a large outgoing expense that almost certainly will not, in most cases, yield end products.¹⁴⁶ Further, casting governments in the role of funding parties *and regulators* of pharmaceutical products will inevitably result in ongoing issues of conflict of interest—potentially pitting expensive safety regulations against the desire for less costly development processes.

Another alternative frequently mentioned is that well-endowed foundations take on the role of funding drug development in order to fulfill organizational objectives of making certain types and classes of drugs more available.¹⁴⁷ The model of public private partnerships has also been offered as a potential approach and occupies a growing place in the pharmaceutical development world.¹⁴⁸

144. This is true even in the U.S. where there is no universal health care; through the Medicare, Medicaid, Department of Defense and Veteran's Administration, the U.S. government actually buys a huge portion of pharmaceutical products.

145. See HOPE, *supra* note 9, at 287–88. In the U.S., the National Institutes of Health and the National Cancer Institute invest large sums in research. As a general matter, however, this investment is in research based activities and there is little capacity in these agencies to actually take a compound through the drug development process.

146. It is unlikely that governments will have a better success rate than that biopharma achieves and indeed, there are many reasons to expect that the success rate of government-run trials will be lower and the costs higher. Government entities may have a hard time picking potential 'winner' candidates and, conversely, may have a hard time stopping losers, especially when doing so will be subject to political pressures in addition to patient advocacy pressures we have now.

147. See HOPE, *supra* note 9, at 288.

148. Mary Moran, *The New Landscape of Neglected Disease Drug Development*, in CURING MALARIA TOGETHER: ANNUAL REPORT 2005 5, available at http://www.mmv.org/IMG/pdf/Full_Report.pdf (providing an example of a "public private partnership working on diseases of the developing

These are issues that continue to be the focus of discussion and study, and will need to be a central part of any effort to move discussion of open source drug development forward.

V. ACHIEVING THE GOALS OF OPEN SOURCE DRUG DEVELOPMENT

As noted earlier, proponents of open source drug development have variously identified two aims for adopting this approach. One is to ensure greater access to the information inputs and outputs of drug development so that there is greater potential for ongoing scientific exchange and innovation. To a large extent, this seems an achievable goal. By definition, open source licensed information is available on a non-exclusive, royalty-free basis, often with the obligation that any derivations or improvement on the ideas are similarly available.

The second goal relating to end products that are less costly and more accessible is a far greater challenge. Utilizing open source drug development to make drugs less costly rests on two significant presumptions: (1) that the research and development costs related to open source drug development will be less than that of conventional drugs, lowering costs that are passed on to purchasers; and (2) that greater competition resulting from the absence of monopoly rights will drive prices down. This section examines this goal further and concludes that neither of these claims will always be true for open source drug development and thus it is not clear that open source drug development will, in all cases, result in lower cost drugs. Nevertheless, the discussion leaves open the possibility that there are situations where open source drug development might result in less costly drugs with the additional benefit of leaving key drug development information available to other licensees and innovators.

A. DEVELOPMENT COSTS

The discussion in Section IV above, suggested that it is possible that drug development costs be reduced. However, the amount of cost reduction, and whether it is enough to significantly lower prices for purchasers, is uncertain. If the

world").

compound being developed is in-licensed under open source terms, costs relating to licensing for that compound at that stage of development would be minimal (i.e., an open source license is generally non-exclusive and royalty-free). The caveat, of course, is that to the extent *non*-open source molecules/compounds need to be licensed into the development process (which raises the specter of IP complications, as discussed above), there could still be significant costs associated with licensing.

There is also a potential for some cost savings at the front end if the drug development is carried out under a virtual pharma model as discussed above, as the need for personnel and overhead may be somewhat reduced. These savings are hard to quantify without knowing the specific needs of the development program in question.

Even with this potential for cost savings, it is important to recognize that the main drivers of drug development costs will exist for open source drug development as well. These include the cost of maintaining GXP compliant laboratories and undertaking pre-clinical studies, which can individually range into the hundreds of thousands of dollars. The costs of clinical trials often range into the millions of dollars and added to that are costs related to preparing a regulatory package.¹⁴⁹ If successful there will be additional expenses related to establishing manufacturing capacity, testing and distribution of products. Ultimately, while the cost per molecule may not be the \$800 million claimed by industry, it will still be significant and require extensive capital resources.

B. PRICE COMPETITION

The second prong of presumed lower costs for drugs developed through open source drug development is that they will be subject to greater competition in the marketplace and hence, prices will be dramatically lower. Specifically, the claim is that without the monopoly rights available to conventionally developed drugs, generic competition will be immediate and will result in very low drug prices.

Conventionally, pharmaceutical companies develop compounds that are the subject of proprietary IP protection. This allows the company a statutory monopoly on the approved

149. DiMasi et al., *supra* note 63, at 162 tbl. 1.

product for some fixed period of time. Depending on the country, the developer may have additional time tacked on to the end of the patent life, either via a patent term extension of half the time taken to get regulatory approval (e.g., under the *Hatch Waxman Act*¹⁵⁰ in the U.S. which grants the drug developer an extension of the patent life of a product to make up for the lengthy duration of drug approval, up to a maximum period of 14 years of patent life plus patent term extension) or via some kind of regulatory exclusivity.

Because open source licensed compounds are, by definition, freely shared, an open source-licensed compound could be licensed to multiple parties at the same time, and all of those licensees could pursue drug development at the same time. Alternatively, competitors could be free to access the open source licensed compound post-approval to apply for generic status at any time.¹⁵¹ That is, there would be no period of exclusivity.

When considering the potential for generic (or any other competition) to a pharmaceutical, it is important to remember that for any drug product, regulatory approval is required prior to marketing.¹⁵² Products cannot simply be placed on the market. Thus, when speculating about increased competition, one also has to consider the costs and incentives for getting to market.

There are two routes for copies of a drug to come to market. The first is that a second party can sponsor a full drug development for the same molecule or compound under Section 505(b)(1) of the U.S. Federal Food, Drug and Cosmetics Act.¹⁵³

150. Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (codified at 15 U.S.C. §§ 68b-68c, 70b (1994); 21 U.S.C. §§ 301 note, 355, 360cc (1994); 28 U.S.C. § 2201 (1994); 35 U.S.C. §§ 156, 271, 282 (1994)).

151. As discussed above, the availability of the final product on OS terms will depend on how other licenses interact with the OS license. It is possible that a subsequent license could force an override of any OS provisions that would share exclusively licensed IP.

152. Post-marketing changes are also heavily regulated. For example: for example, notice to regulators has to be made for all changes in manufacturing, safety information, drug interaction information and the like. Depending on the type of change, approval by regulators must be obtained before doing it.

153. 21 U.S.C. § 355(b) (2006); DONALD O. BEERS, *GENERIC AND INNOVATOR DRUGS: A GUIDE TO FDA APPROVAL REQUIREMENTS* § 4.02, at 4–3 to 4–56 (6th ed. 2004).

In the case of open source drug development, two parties could presumably license the molecule or compound and do the necessary studies for submission. This approach requires full costs for each party.

The second avenue is as a generic version of the drug, under an abbreviated drug approval process. Generic drugs may be approved by regulators when the patent term and relevant regulatory exclusivities have expired.¹⁵⁴ Abbreviated submissions generally require GXP compliant evidence of bioequivalence, as well as evidence of manufacturing capabilities. Generic manufacturers also have post-marketing safety reporting obligations and are subject to similarly tight controls on ingredient quality, sourcing, and other manufacturing issues.¹⁵⁵ While these requirements are certainly not as extensive as those required for the first approved reference drug, they do require that a sponsoring company has specific capacities in the pharmaceutical sector.

Prices of drugs generally drop once a generic drug competitor is introduced. The magnitude of the drop in prices is a function of how much competition there is. The introduction of a single generic, for example, generally only causes a price drop of under 30%, while the price can drop more substantially when there are multiple competitors.¹⁵⁶ As a general rule, pricing of generic drugs is a reflection of market competition—or, in countries, where drug prices are regulated—of prices set by relevant authorities.

Importantly, the potential for increased competition does not *per se* guarantee that open source developed drugs will be cheap. If only one entity takes the drug through to marketing authorization, that entity will have a monopoly by default and can set the prices per market rates—or per national pricing authorities (or, of course, based on market access levels). At the same time, it is *possible* that if the product is profitable or there is a potentially large market for it, other competitors may come on the market as generics. But it is also possible that the size of the market—or any number of other factors including availability of active ingredients, marketing costs, potential

154. 21 U.S.C. § 355(j) (2006).

155. 21 C.F.R. § 314.81 (2009).

156. See Henry G. Grabowski & John M. Vernon, *Brand Loyalty, Entry, and Price Competition in Pharmaceuticals After the 1984 Drug Act*, 35 J.L. & ECON. 331, 336 (1992).

liabilities or other factors—could make generic development unattractive to other parties. There are numerous instances where the brand company that initially obtained approval for a drug remains the only manufacturer of that product despite the expiration of patents.

Also, there can be considerable variation in the amount of price reduction that results from generic entry. If the cost of manufacturing remains high because of costs of ingredients or processes, the end product is likely to be costly as well. Finally, although it may appear natural to look to generic companies to engage in open source drug development, that would be an entirely new role for such companies. Generic companies currently produce drugs that have already been proven safe and effective, and such companies enter proven markets that have years of history. In contrast, generic companies attempting to develop a new drug that is open source based would be taking on new risk much greater than they now face. It is far from clear that many would do so.

C. POSSIBLE SCENARIOS?

It is possible that a philanthropic consortium dedicated to improving access for a specific therapeutic area could fund an open source drug development program with the aim of developing the drug at low cost and seeding the field for generic competition. If that organization chose a drug with a large potential market, it is likely that a generic marketplace would emerge for the drug. The program could be further supported by making sure relevant manufacturing technology transfer was also available to potential competitors.

The potential benefits of such a program are multi-faceted. First, the consortium would be undertaking the significant investment of developing a (needed) drug. It would be doing so while allowing other researchers to continue using the relevant compound, thus enabling the possibility of additional innovation. Further, the consortium would be putting together a package that others could rely on for abbreviated approvals to make the same drug at potentially cheaper prices. It is possible that the number of potential purchasers of generic versions of the drug offers sufficient incentives to generic companies to manufacture copies of the drug that would be sold for less. If that happened, the consortium would, arguably, have created a self-sustaining system for accessible drugs without, necessarily,

having to invest in long term access for the drug. That said, the consortium would still have had to invest the up front costs to undertake drug development. In addition, there are questions of scope and sustainability: given the large amount of resources required, it is unclear how many such initiatives could be undertaken and for how long.

Other scenarios that have been suggested are various kinds of public-private partnerships and new types of corporations that have explicit social requirements built into their structure.¹⁵⁷ An example of the latter is the Community Interest Company (CIC), which was first enacted into law in the United Kingdom in 2005.¹⁵⁸ These corporations are designed to appeal to investors who are willing to cap their financial rewards on the grounds that the company is making a significant, identifiable social contribution.¹⁵⁹ So far, such companies have not appeared in a significant way in the biopharmaceutical sector, but it would seem that if the need to maximize profits is somewhat offset by social goals, there is at least in principle the possibility that such companies could offer their products at lower cost and thus increase accessibility.

VI. INTERIM CONCLUSION: WHAT IS THE FUTURE OF OPEN SOURCE DRUG DEVELOPMENT?

Conceptually, open source drug development is presented as a route for ensuring that the open source-licensed IP related to drug development remains available and for greater access to healthcare products. However, as described in this article, open source drug development would involve complex IP relationships, a lengthy and expensive development process, novel and potentially difficult management, staffing and financing, while at best offering uncertain impacts on cost and accessibility. It is difficult to imagine a system so encumbered being widely adopted for drug development and it seems

157. I credit Ed Levy with developing this line of thought.

158. Community Interest Company Regulations 2005, S.I. 2005/1788 (U.K.).

159. Fraser Valley Centre for Social Enterprise, Analysis of L3C and CIC Social Enterprise Models, <http://www.centreforsocialenterprise.com/index.html> (follow “2. For a Centre document outlining the characteristics of the US and UK legal models for social enterprise” hyperlink), at 5 (last visited, June 1, 2009); *see also* List of Community Interest Companies, <http://www.cicregulator.gov.uk/coSearch/companyList.shtml> (last visited, Oct. 22, 2009).

unlikely that a private company would be interested in taking on such a process.

Despite these hurdles, the goals of open source drug development remain worthy and should be the subject of further discussion. In order to advance the conversation further, this article closes with brief comments on: (1) whether there are more targeted uses of open source that might be more readily adopted, (2) whether additional incentives could overcome some of the hurdles identified and spur adoption of open source practices in drug development, and finally (3) whether there are alternative pathways to the goals underlying open source drug development.

A. DIAGNOSTICS AS A POTENTIAL MODEL AREA FOR OPEN SOURCE DEVELOPMENT

Diagnostics are tools which indicate the presence or absence of a disease or potential treatment possibilities for a certain type of disease.¹⁶⁰ Such tools are increasingly prevalent with the emergence of personalized medicine, which aims for targeted use of therapeutic products.

Currently, in the U.S. laboratory-developed diagnostic assays¹⁶¹—those assays for which a blood, urine, or DNA (or other) sample is sent away to a lab for analysis (as opposed to a kit sold on the market)—are not subject to the same standards of regulation as drugs or biologics. In fact, at present in the U.S., such assays must only be compliant with standards that require that there is analytic validity, meaning that the tests must yield the same results each time.¹⁶² There is no pre-

160. In-Vitro diagnostic is defined in 21 C.F.R. § 809.3 (2009).

161. A laboratory-developed assay is one developed by a clinical laboratory for use only by that facility. Diagnostics are regulated as a subset of the medical device category. *See* 21 U.S.C. §321(h) (2009). Therefore, diagnostics are subject to a different regulatory regime than drugs and biologics. *See, e.g.*, 21 U.S.C. §360(c), (e). Laboratory-developed assays represent a very small subset of the medical device, or diagnostic, categories. Nevertheless, they are of particular interest for purposes of this discussion because of their uncertain and shifting regulatory oversight.

162. The relevant standards in the U.S. are the Clinical Laboratory Improvement Act (CLIA), Pub. L. No. 90-174, 81 Stat. 533, and related regulations administered by the Department of Health and Human Services. *See* 42 C.F.R. pt. 493 (2008). While CLIA establishes certain laboratory standards, e.g., for certification, quality assurance, quality control and personnel, it provides minimal standards for assessment of analytical validity

market safety or efficacy review in a manner analogous to what is required of drugs.¹⁶³ Further, competitor tests can come on the market with exactly the same minimal regulatory hurdle as long as there is no proprietary position barring that entry. There is no “generic” pathway or approval needed.

Despite this much less burdensome regulatory regime, diagnostics can be very expensive and inaccessible because patent exclusivity allows companies to charge monopoly prices.¹⁶⁴ Hypothetically, open source licensing of the underlying IP could change this situation. If the underlying IP were licensed out on open source terms, multiple parties could develop the same or competitor diagnostic products and the cost of such products should drop. Given the relatively low costs of putting such diagnostics on the market in terms of regulation, the potential revenue from charging parties to run the assay may provide enough financial incentive for parties to continue to develop the tests.

As discussed *supra*, the IP landscape on any given product may be complex. If a diagnostic were based on a single open source licensed patent, it too would be available on open source terms. However, many diagnostic assays are algorithm based, meaning that they rely on relationships between the presence and activity of multiple genes—and likely multiple patents—to make probabilistic assessments about the likelihood of a disease or condition. As explored in Section IV.A, above, it would be difficult to establish open source licensing for all relevant inputs and the interplay of open source and non-open source licenses would likely be complex. This is, however, a topic worth further exploration.

B. ADDITIONAL INCENTIVES

It may also be worth considering the introduction of

and no standards for the assessment of clinical validity (i.e. efficacy).

163. In the past several years, the FDA has been evaluating whether it should change these practices and has issued a draft guidance proposed that certain laboratory based diagnostic assays be subject to PreMarket Approval (21 C.F.R. § 814), like certain other medical devices. *See* FDA, Draft Guidance for Industry, Clinical Laboratories, and FDA Staff—In Vitro Diagnostic Multivariate Index Assays, <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm079148.htm> (last visited Jan. 28, 2010).

164. E. RICHARD GOLD & JULIA CARBONE, MYRIAD GENETICS: IN THE EYE OF A POLICY STORM 25 (2008), available at <http://ssrn.com/abstract=1260098> (follow “download” hyperlink).

additional incentives to foster adoption of open source licensing in the biomedical sciences. The rationale is that a greater number of open source licenses increases access to information overall and makes it easier to combine multiple licenses to create an open source product.

For example, one could introduce a new form of data exclusivity, administered by a regulator, that rewards drug development of an open source licensed molecule, pathway or process.¹⁶⁵ In the short term, the data exclusivity would allow the drug developer a certain fixed term of market monopoly, by blocking others from relying on the approval data to file a generic application. This would allow the drug developer a fixed term to recoup some of its investment. The benefit of using data exclusivity rather than a patent would be that the underlying IP would remain under open source terms and available for use by others in ongoing research and innovation.

A data exclusivity awarded to open source drug development would stand in the way of price reductions due to generic competition. However, after the course of the data exclusivity, generics would also be able to rely on the original submission to regulators in their abbreviated applications.

C. OTHER ALTERNATIVES TO ACHIEVE SIMILAR ENDS

Even as open source drug development continues to be explored, it is worth considering other alternatives to achieve similar ends. As discussed above, there are two potential co-existing aims for using open source in drug development, namely: (1) to keep the knowledge inputs into drug development available for use without IP barriers, and (2) to make healthcare products less costly and more accessible.

With respect to the first goal, there are other potential options to keeping material available to other researchers and drug developers. For example, at present there exists a “research exemption” from patent infringement available to

165. My colleague Ed Levy initially suggested this idea in the context of open source to me. *See also* HOPE, *supra* note 9, at 215 (stating that exclusive marketing rights obtained by FDA approval may provide “[sufficient] incentive to induce commercial actors to engage in the more costly aspects of integration while still not being a strong enough proprietary or quasi proprietary right to deter upstream contributions”). For a discussion of the role of FDA exclusivities on innovation, see Rebecca Eisenberg, *The Role of the FDA in Innovation Policy*, 13 MICH. TELECOMM. & TECH. L. REV. 345 (2007).

those using patented information for purely research, non-commercial ends.¹⁶⁶ In recent years, courts—particularly in the U.S.—have blurred the lines of this exemption and suggested that any research that could potentially ultimately have commercial uses, is outside the exemption.¹⁶⁷ These decisions have complicated reliance on a research exemption for researchers. Simply clarifying and codifying a broad research exemption through legislation could potentially go a long way toward making patented information available to a wide base for ongoing knowledge development. One can speculate as well that reducing licensing costs for inputs to drug development—if applicable—could yield some reduction in the overall costs of drug development. However, such cost reductions are likely to be minimal in contrast to the required regulatory elements.

Another option, which may address both goals of open source, is targeted use of patent pools. Patent pools aim to make a certain set of intellectual property available in an effort to overcome the potential of patent thickets or other IP blocks. In a forthcoming article,¹⁶⁸ my colleagues develop the argument that patent pools might be used as a tool to promote open science and access to information. In this context, it is worth exploring further how patent pools may similarly make drug development more accessible and less costly (with the same caveat as above, that the costs of completing required regulatory elements remains very high). GlaxoSmithKline (GSK) recently announced that they would make certain patents available publicly in a “pool” to promote development of drugs for neglected diseases.¹⁶⁹ While one could question

166. 35 U.S.C. § 271(e)(1) (2006). To encourage development and expedite the introduction of pharmaceuticals into the marketplace, Congress amended the patent laws in 1984 to insulate drug research from charges of infringement so long as such research is “solely for uses reasonably related to the development and submission of information” to FDA. Thus, activities that would otherwise constitute patent infringement noninfringing if they are undertaken for the purpose of developing and submitting to the FDA information necessary to obtain marketing approval for a new chemical entity, a medical device, or a food additive.

167. Merck KGaA v. Integra Lifesciences I, Ltd., 545 U.S. 193 (2005); *Madey v. Duke Univ.*, 307 F.3d 1351 (Fed. Cir. 2002). Taken together, these cases suggest that any research that has ultimate commercial aims does not fall under the research exemption. The impact of these cases continues to be the subject of legal discussion and interpretation.

168. Ed Levy et al., *Patent Pools and Genomics: Navigating a Course to Open Science?*, 16 B.U. J. SCI & TECH L. 75 (2010)

169. Andrew Witty, CEO, GlaxoSmithKline, Speech to Harvard Medical

whether the GSK arrangement fits the definition of a patent pool, we think this variation should be explored further as a potential avenue for furthering drug development in certain areas. It may be that novel financing or tax tools, in combination with some form or variation of patent pools, provides an appropriate and workable path to less expensive and more accessible drugs.

A third approach would be to develop licensing strategies that permit greater access for certain uses—for example, for drug development for neglected disease or use by those in the developing world.¹⁷⁰ The idea, again, is to reduce the intellectual property costs associated with drug development in an effort to reduce the cost and promote accessibility to the resulting drug product.

In addition to these alternative approaches to intellectual property, there are other novel mechanisms that could be considered to reach similar goals. These could include novel regulatory approaches that might streamline the regulatory obligations in certain situations, alternative regulatory incentives, and the potential for developing greater access to abandoned drug development programs. Greater thought and attention is needed in each of these areas.

The ultimate goal of making drugs less costly and more accessible through the application of alternative IP regimes is a good one. However, any such attempt is far from simple. The IP landscape of drugs is highly complex and any attempt at change must be weighed against a web of regulation and other legal requirements. There is hope, however, that a carefully considered combination of changes to IP, financing—and possibly regulation—can achieve the goal.

School: Big Pharma as a Catalyst for Change (Feb. 13, 2009), *available at* <http://www.gsk.com/media/Witty-Harvard-Speech-Summary.pdf>.

170. See Jean O. Lanjouw, *A New Global Patent Regime for Diseases: U.S. and International Legal Issues*, 16 HARV. J.L. & TECH. 85, 106–11 (2002).