

# BIOPROSPECTING AND BIODIVERSITY CONSERVATION: WHAT HAPPENS WHEN DISCOVERIES ARE MADE?

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*There has been extensive debate over whether private-sector bioprospecting for pharmaceutical compounds creates significant incentives for biodiversity conservation. We offer a case study of the discovery and commercial development of the anti-cancer drug taxol from the Pacific yew tree, highlighting neglected issues in the debate over bioprospecting and conservation incentives. The discovery of taxol and the search for taxol-like compounds illustrates how bioprospecting can substitute threats to biodiversity from over-harvesting for threats to biodiversity from habitat conversion. As this example illustrates, whether creation of market demand for genetic resources encourages or discourages biodiversity conservation depends crucially on underlying property rights.*

## INTRODUCTION

There has been extensive debate over whether private-sector bioprospecting for pharmaceutical compounds creates significant incentives for conservation of biological diversity. This Article examines how an actual discovery of a medically and economically important compound affected a range of conservation incentives. We offer a case study of the discovery and commercial development of the anti-cancer drug taxol from the Pacific yew tree, highlighting some neglected issues in the debate over bioprospecting and conservation incentives. The discovery of taxol and the search for taxol-like compounds illustrates how bioprospecting can substitute threats to biodiversity from over-harvesting for threats to biodiversity from habitat conversion. As this example illustrates, whether creation of market demand for genetic resources encourages or

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discourages biodiversity conservation depends crucially on underlying property rights.

## I. BIOPROSPECTING, PROPERTY RIGHTS, AND BIODIVERSITY CONSERVATION

Bioprospecting is the search among living organisms for compounds that have commercial value as active ingredients in pharmaceuticals, pesticides, and other products. Natural products, derived from plants and animals, remain a basic source of many pharmaceuticals. Soejarto and Farnsworth estimated that roughly a quarter of prescription drugs contain some natural products.<sup>1</sup> This percentage increases when one considers traditional medicines used in developing countries.<sup>2</sup> Despite advances in chemistry and biotechnology, production of these drugs via synthesis, tissue culture, or genetic manipulation often remains uneconomical. The anti-malaria drugs quinine and quinidine, for example, are still produced from chinchona bark. Madagascar's rosy periwinkle, *Catharansus roseus*, remains the basic ingredient in the anti-cancer drugs vincristine and vinblastine, as well as the anti-hypertension drug ajmalicine. Artemisinin, used to treat drug-resistant malaria, is produced through semisynthesis using material isolated from the shrub *Artemisia annua*, long used in traditional Chinese medicine.<sup>3</sup> Semisynthesis uses large, complex molecules isolated from plants, animals or bacteria as building blocks to produce a wide range of drugs and other chemicals.<sup>4</sup>

In addition to providing raw materials for medicines, natural products also provide information for pharmaceutical development: the molecular structures of natural products serve as blueprints or as leads in developing compounds. Millions of years of evolution have led to molecules organic chemists would not dream of producing. These molecules often have novel mechanisms of action against diseases. With advances in biotechnology, the scope for using this genetic information to develop new medicines has increased. Wildlands, where species reside, have an option value as a potential source of genetic materials and information.

Biodiversity as a source of medical breakthroughs has drawn considerable attention from the medical and environmental communities.<sup>5</sup> The Earth's

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1. D.D. Soejarto & N.R. Farnsworth, *Tropical Rainforests: Potential Sources of New Drugs*, 32 PERSP. BIOLOGY & MED. 244, 246 (1989).

2. Walter Reid, *Biodiversity and Health: Prescription for Progress*, 37 ENVIRONMENT 14-15 (1995).

3. Edward M. Croom, Jr., *Taxus for Taxol and Taxoids*, in TAXOL®: SCIENCE AND APPLICATIONS 37, 38 (Matthew Suffness ed., 1995).

4. K. C. Nicolaou, Rodney K. Guy & Pierre Potier, *Taxoids: New Weapons against Cancer*, 274 SCI. AM. 96, 97 (1996).

5. See, e.g., Elissa Blum, *Making Biodiversity Conservation Profitable: A Case Study of the Merck/INBio Agreement*, ENVIRONMENT, May 1993, at 17 (1993); Thomas Eisner, *Prospecting for Nature's Chemical Riches*, ISSUES SCI. AND TECH., Winter 1989-1990, at 31; Sarah A. Laird, *Contracts for Biodiversity Prospecting*, in BIODIVERSITY PROSPECTING: USING GENETIC RESOURCES FOR SUSTAINABLE DEVELOPMENT 99, 99-130 (Walter V. Reid et al. eds., 1993); Walter V. Reid, *Biodiversity and Health: Prescription for Progress*, ENVIRONMENT, July-Aug. 1995, at 12; Leslie Roberts, *Chemical Prospecting:*

biodiversity may be thought of as a vast, unexplored library with information leading to many possible medical breakthroughs. The total number of species on the planet is unknown, and only a small number have been screened for medical activity. Further, the medical screening process has improved over time, so compounds thought to be of little value at one time may turn out to be quite important later. Based on sheer numbers, areas rich in biodiversity, such as tropical rainforests, appear promising for exploration of new drugs. Biologists estimate that the tropics are home to most of the world's plant and animal species, with the tropical forests especially rich in species.<sup>6</sup> Mendelsohn and Balick identified forty-seven major pharmaceuticals derived from compounds from tropical flowering plants.<sup>7</sup> Extrapolating from past discoveries and estimates of species numbers, they estimated that over 300 undiscovered drugs remain in tropical forests and that these drugs are worth \$147 billion to society.<sup>8</sup>

Yet, 42 million acres of tropical forests are cleared annually, primarily for subsistence agriculture and cattle ranching,<sup>9</sup> and the resulting habitat conversion is considered the primary cause of biodiversity loss.<sup>10</sup> These circumstances beg the question: if genetic resources have such value (actual or potential) for pharmaceutical development, why are they being depleted so quickly? While conserving genetic resources that are potential sources of new medicines may make sense from a social perspective, private decision-makers may often lack incentives to do so.

While natural products have been important sources of pharmaceutical materials and information, historically the pharmaceutical industry has hesitated to engage in much collecting and testing of genetic materials. This reluctance may stem from public-good aspects of information about the value of genetic materials.<sup>11</sup> A firm collecting and screening biological samples would have difficulty excluding others from the information that a sample showed promising medical activity. This would be particularly true as a compound's origins, mechanism of action, and efficacy were revealed through required disclosures during the drug-development application process and through clinical trials. Although the knowledge of a compound's medical activity may be valuable, firms

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*Hope for Vanishing Ecosystem?*, 256 SCIENCE 1142, 1142-43 (1992); Soejarto & Farnsworth, *supra* note 1, at 244-251; Christopher J. Hunter, Comment, *Sustainable Bioprospecting: Using Private Contracts and International Legal Principles and Policies to Conserve Raw Medicinal Materials*, 25 B.C. ENVTL. AFF. L. REV. 129 (1997).

6. Stuart Pimm & Peter Raven, *Extinction by Numbers*, 403 NATURE 843, 844 (2000); E.O. Wilson, *The Current State of Biological Diversity*, in BIODIVERSITY 8 (E.O. Wilson ed., 1988).

7. Robert Mendelsohn & Michael J. Balick, *The Value of Undiscovered Pharmaceuticals in Tropical Forests*, 49 ECON. BOTANY 223, 224 (1995).

8. *Id.* at 225.

9. Nancy R. Forster, *Protecting Fragile Lands: New Reasons to Tackle Old Problems*, 20 WORLD DEV. 571, 571 & n.1 (1992).

10. Pimm & Raven, *supra* note 6, at 844; Wilson, *supra* note 6, at 10, 27.

11. Gardner M. Brown & Joseph Swierzbinski, *Endangered Species, Genetic Capital and Cost-Reducing R&D*, in ECONOMICS OF ECOSYSTEMS MANAGEMENT 111, 113 (David Oakly Hall, Norman Myers & N.S. Margaris eds., 1985); Roger Sedjo, *Property Rights, Genetic Resources, and Biotechnological Change*, 35 J.L. & ECON. 199, 200-01 (1992).

have an incentive to free-ride off the search and discovery activities of others. Thus, expected private economic gains to bioprospecting by individual companies are considerably less than social gains.

Another disincentive for natural product collection and screening can be traced to historically weaker intellectual property protection for biological innovations, compared with mechanical or chemical innovations. The mere discovery of a new plant, animal, or other organism found in the wild cannot be patented. This legal rule limits firms' abilities to exclude others from access to raw genetic materials once discovery becomes known. Because of these disincentives for private sector collection, large-scale, sustained search and screening of plant and animal materials for medical or agricultural applications historically has been carried out by the public sector.

Tropical countries have also been unable to exercise intellectual property rights and capture gains from products developed from their raw genetic materials. For example, while Eli Lilly, maker of vinblastine and vincristine, derived from Madagascar's rosy periwinkle, earned \$100 million per year from these drugs. Madagascar, the source of the raw materials, received no royalties from sale of the drug.<sup>12</sup>

Yet another disincentive for conservation is competing demands for lands that serve as wildlife habitats. Returns to these other uses (such as timber harvesting, farming, or ranching) represent opportunity costs of habitat preservation. In principle, forests could be used as extractive reserves where medicinal plants (and other products) are harvested renewably. In a study of Belize, Balick and Mendelsohn estimate that returns from such an extractive reserve (at least over a small area) could yield returns that compare favorably with agricultural production.<sup>13</sup> In many other instances, however, incentives for land clearing simply outweigh conservation incentives. This imbalance may stem from poverty and insecurity of tenure on tropical land frontiers,<sup>14</sup> from active government policies to encourage land conversion,<sup>15</sup> or from both.

In the 1980s and 1990s, technological and institutional changes led to increased incentives for and renewed interest in natural product development. Advances in biotechnology have increased the ability of scientists to genetically engineer new organisms.<sup>16</sup> In *Diamond v. Chakrabarty*, the Supreme Court ruled that organisms bred or genetically modified for novel traits could be patented.<sup>17</sup>

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12. Kelly Day-Rubenstein & George B. Frisvold, *Genetic Prospecting and Biodiversity Development Agreements*, 18 LAND USE POL'Y 205, 208 (2001).

13. Michael J. Balick & Robert Mendelsohn, *Assessing the Economic Value of Traditional Medicines from Tropical Rain Forests*, 6 CONSERVATION BIOLOGY 128, 129-30 (1992).

14. George B. Frisvold & Peter Condon, *Biodiversity Conservation and Biotechnology Development Agreements*, 12 CONTEMP. ECON. POL'Y, July 1994, at 1, 5.

15. Hans P. Binswanger, *Brazilian Policies that Encourage Deforestation in the Amazon*, 19 WORLD DEV. 821, 821-28 (1991).

16. Robbin Shoemaker et al., *Economic Issues in Agricultural Biotechnology*, AGRICULTURE INFORMATION BULLETIN NO. AIB762, at 12-16 (2001).

17. *Diamond v. Chakrabarty*, 447 U.S. 303, 318 (1980).

The U.S. Patent and Trademark Office extended the Supreme Court's decision, ruling that utility patents could be awarded for human-developed traits in plants<sup>18</sup> and animals.<sup>19</sup>

Not only did United States law redefine property rights in natural products; international agreements took part in this shift as well. Historically, it was common practice for botanists or plant scientists to send materials back to their home countries for screening without the knowledge or consent of the country of origin.<sup>20</sup> The United Nations Convention on Biological Diversity, which entered into force on December 29, 1993, seeks to change that practice. Article 15 of the Convention asserts that (a) countries have sovereign rights to their genetic resources (section 1), (b) access to genetic resources shall be subject to prior informed consent of the source country (section 5), and (c) access shall be on mutually agreed terms (section 4).

In addition, Article 15 (7) of the Convention states:

Each Contracting Party shall take legislative, administrative or policy measures . . . with the aim of sharing in a fair and equitable way the results of research and development and the benefits arising from the commercial and other utilization of genetic resources with the Contracting Party providing such resources. Such sharing shall be upon mutually agreed terms.<sup>21</sup>

This provision formalizes the right of a country to use its property rights over genetic resources to gain a greater share of the benefits from technologies using those resources.

Another indication of the international shift is the Uruguay Round of the General Agreement on Tariffs and Trade (GATT); it was finalized in 1994 and created minimum standards for intellectual property protection for commercially developed seed and plant varieties.<sup>22</sup> Article 27, 3(b) states, "Members shall provide for the protection of plant varieties either by patents or by an effective *sui generis* system or by any combination thereof."<sup>23</sup>

In the wake of these redefinitions of property rights over both naturally occurring and human-modified genetic resources, a number of biologists and conservationists have touted bioprospecting arrangements as ways to

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18. *Ex parte* Hibberd, 227 USPQ 443 (B.P.A.I. 1985).

19. *Ex parte* Allen, 2 USPQ 2d 1425, 1427 (B.P.A.I. 1987).

20. United Nations Conference on Environment and Development: Convention on Biological Diversity, June 5, 1992, 31 I.L.M. 818.

21. *Id.* at 828.

22. Agreement on Trade-Related Aspects of Intellectual Property Rights, April 15, 1994, General Agreement on Tariffs and Trade: Multilateral Trade Negotiations Final Act Embodying the Results of the Uruguay Round of Trade Negotiations, Annex 1C, 33 I.L.M. 1125, 1197.

23. *Id.*

simultaneously develop medicines and improve conservation incentives by allowing developing countries to capture gains from new product development.<sup>24</sup>

Indeed, a number of bioprospecting arrangements reflecting these trends have arisen. The most studied was one between the pharmaceutical multinational Merck, the Instituto Nacional de Bioversidad ("INBio"), a Costa Rican non-profit private organization, and the government of Costa Rica.<sup>25</sup> The agreement originally was a two-year collection contract, in which INBio received a \$1 million payment plus more than \$100,000 in equipment. INBio scientists received technical training locally and at Merck facilities. INBio was also to receive an undisclosed percentage of royalty payments for any discoveries Merck made, to be shared with Costa Rica's Ministry of Natural Resources. Merck retained first rights to patent discoveries, however.<sup>26</sup> In February of 1997, the agreement was renewed, with Merck expected to provide an additional \$1 million in research funds during 1997 and 1998.<sup>27</sup> In addition, INBio was paid for sample collection and processing. The Costa Rican government and INBio also cooperated with Cornell University and Bristol-Myers Squibb to collect and screen insects as a source of drugs.<sup>28</sup>

Federal government agencies in the United States have also attempted to encourage bioprospecting agreements. In 1992, the U.S. Agency for International Development implemented a program encouraging joint biodiversity research and development between developing countries and private industry.<sup>29</sup> The U.S. National Cancer Institute ("NCI") has entered into contracts with organizations in Madagascar, Tanzania, Zimbabwe, and the Philippines, while the British firm Biotics has signed agreements with organizations in Ghana and Malaysia.<sup>30</sup>

The International Cooperative Biodiversity Group ("ICBG") was initiated by the U.S. National Institute of Health ("NIH"), the U.S. National Science Foundation, and the U.S. Agency for International Development in 1993 to promote drug discovery, biodiversity research, and conservation by funding research consortia and encouraging royalty payments to developing countries in

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24. See, e.g., Blum, *supra* note 5, at 41–44; Eisner, *supra* note 5, at 31–34; Laird, *supra* note 5, at 99–100; Reid, *supra* note 5, at 36–39; Roberts, *supra* note 5, at 1142–43.

25. See, e.g., Blum, *supra* note 5, at 38–40; Day-Rubenstein & Frisvold, *supra* note 12, at 214–17; Frisvold & Condon, *supra* note 14, at 1–2, 6–8; Roberts, *supra* note 5, at 1142–43; Anna Sittenfeld & Rodrigo Gomez, *Biodiversity Prospecting by INBio, in BIODIVERSITY PROSPECTING: USING GENETIC RESOURCES FOR SUSTAINABLE DEVELOPMENT* 69–98 (W.V. Reid et al. eds., 1993); R. David Simpson & Roger A. Sedjo, *Commercialization of Indigenous Genetic Resources*, CONTEMP. ECON. POL'Y 34, Oct. 1994, at 34–43.

26. Blum, *supra* note 5, at 20.

27. Day-Rubenstein & Frisvold, *supra* note 12, at 215.

28. Joshua Rosenthal, *Integrating Drug Discovery, Biodiversity Conservation, and Economic Development: Early Lessons from the International Cooperative Biodiversity Groups*, in *BIODIVERSITY AND HUMAN HEALTH* 281, 284–85 (Francesca Grifo & Joshua Rosenthal eds., 1996); Day-Rubenstein & Frisvold, *supra* note 12, at 215.

29. JOEL I. COHEN, *CONSERVATION AND USE OF AGRO-ECOLOGICAL DIVERSITY* 13 (1992).

30. Simpson & Sedjo, *supra* note 25, at 34, 41.

the event of discoveries.<sup>31</sup> Since then, they have financed several consortia of government agencies in developing countries, U.S. universities, and private firms.

As these examples illustrate, the terms of these bioprospecting agreements often vary greatly. A source country may simply provide access to natural resources, or it can provide complete prospecting services, such as screening and evaluating the samples. Agreement terms also depend on search strategy. Drug prospecting entails collecting samples that are screened for activity against a certain disease (e.g., cancer or AIDS). Prospecting can focus on random collections of plants or other living things. Drug companies often prefer random collection because it yields more diverse samples.<sup>32</sup> Prospecting can also be targeted, with collectors using ethno-botanical or ethno-medical information to narrow the search.<sup>33</sup> Targeted samples are usually collected and screened on a slower, smaller scale. In this type of prospecting, the source country often supplies traditional knowledge.<sup>34</sup>

The methods of compensating source countries vary and can be complex. In the simplest model, the source country is paid a fee for samples. Often, agreements provide the source country with royalties from the sale of a successful product, should one be developed. Here, the source country faces the possibility that such a compound may not be found, and thus, no royalty payments may be received.<sup>35</sup> Royalty provisions often have an inverse relationship with up-front payments: the larger the up-front payments, usually the smaller the royalty rate.<sup>36</sup>

A more complex model involves the use of ethno-botanical or ethno-medical data, which can raise complicated intellectual property rights issues over how suppliers of traditional knowledge are compensated.<sup>37</sup> A royalty scheme may become further complicated if indigenous knowledge was used to select the sample and the sale of the product takes place some time in the future. For example, identifying which group or groups initially developed the knowledge may be difficult to identify. Determining who has a right to compensation for "traditional" knowledge could also be difficult.<sup>38</sup> Other forms of compensation

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31. JOHN E. FOGARTY INT'L CTR. FOR ADVANCED STUDY IN THE HEALTH SCIS., FOGARTY AT 35, at 41 (Joan Wilentz ed., 2003), available at <http://www.fic.nih.gov/about/history.pdf>.

32. Day-Rubenstein & Frisvold, *supra* note 12, at 208.

33. Blum, *supra* note 5, at 40–41; David Downes, *How Intellectual Property Could Be a Tool to Protect Traditional Knowledge*, 25 COLUM. J. ENVTL. L. 253, 254–55 (2000); Laird, *supra* note 5, at 119–20.

34. Steven M. Rubin & Stanwood C. Fish, *Biodiversity Prospecting: Using Innovative Contractual Provisions to Foster Ethnobotanical Knowledge, Technology and Conservation*, 5 COLO. J. INT'L ENVTL. L. & POL'Y, 23, 52 (1994).

35. Royalties are percent of future, uncertain sales if a discovery is made. More assured, up-front payments have become increasingly important to developing countries that, as a group, operate on limited financial means. Day-Rubenstein & Frisvold, *supra* note 12, at 208; Laird, *supra* note 5, at 110–11.

36. Rubin & Fish, *supra* note 34, at 52.

37. *Id.*

38. For more discussion of compensation of traditional knowledge, see David Downes, *supra* note 33; Rubin & Fish, *supra* note 34, at 23–40.

may include technology transfer, training, job opportunities, and the right of first refusal as supplier of the resource.<sup>39</sup>

To summarize thus far, biologists and conservationists suggest bioprospecting contracts can simultaneously find new medical breakthroughs and provide developing countries with economic incentives to conserve genetic resources. Advances in biotechnology and changing definitions of intellectual property rights over biological innovations have spurred a number of bioprospecting arrangements. These arrangements, however, are multi-faceted and complex. We turn now to economic assessments of the potential for bioprospecting contracts to encourage biodiversity conservation.

## II. ECONOMIC ASSESSMENTS OF BIOPROSPECTING CONTRACTS

While many biologists and environmentalists have seen bioprospecting agreements as avenues to improve incentives for habitat conservation, economists, by and large, have taken a more skeptical view. Simpson et al. noted that while biodiversity *as a whole* is extremely valuable, for bioprospecting, it is the value of a *marginal* species that matters.<sup>40</sup> They argued that this marginal value of habitat will be low (e.g. \$21/hectare).<sup>41</sup> When several species produce the same chemical compound, the probability of discovering the compound's value is high, but discovery in one species will render other species redundant as a source of that compound. In cases where a compound is rarely found (for example, in one and only one species), the probability of finding a useful lead will be quite small.

Rausser and Small, in contrast, found that marginal values of species from bioprospecting could be large (over \$9,000/hectare).<sup>42</sup> In such cases, private bioprospecting contracts could indeed create incentives to conserve biological diversity. Rausser and Small attribute this difference to the role of information search process. While Simpson et al. assume a random search process, Rausser and Small assume that prospectors can use information to carry out more efficient searches. By using scientific information, one could search for bioprospecting leads in a more efficient order instead of carrying out random searches. This targeting—so their argument goes—raises the value of new searches at the margin. An important policy implication of this argument is that investment in scientific information can stimulate biodiversity-conserving contracting agreements.<sup>43</sup>

Costello and Ward have examined the role of information and search processes on marginal values of biodiversity-rich habitats, explicitly comparing the

39. Rubin & Fish, *supra* note 34, at 29–30, 36–40.

40. The word “marginal,” here, refers to the incremental contribution of one species to making a commercial discovery. R David Simpson, Roger A. Sedjo & John W. Reid, *Valuing Biodiversity for Use in Pharmaceutical Research*, 104 J. POL. ECON. 163, 163 (1996).

41. *Id.*

42. Gordon C. Rausser & Arthur A. Small, *Valuing Research Leads: Bioprospecting and the Conservation of Genetic Resources*, 108 J. POL. ECON. 173, 193 (2000).

43. *Id.* at 176–77.



models and results of Simpson et al. and Rausser and Small.<sup>44</sup> Based on numerical values assumed in both studies, they calculated the marginal value of land in biodiversity hotspots for both random searches (as in Simpson et al.) and optimal searches (as in Rausser and Small). Costello and Ward found that use of information in the search process did raise marginal values, but that increase accounted for only 4% of the difference in the results of the two studies. The bulk of the difference came from different assumptions about other parameter values used in their models. Costello and Ward then derive ranges of estimates of the marginal value of habitat using ranges of parameter values from existing literature. Based on this exercise, their results support Simpson et al.'s assertion that the marginal value of land under bioprospecting would be low and insufficient to counter conversion incentives.<sup>45</sup> Allowing for more efficient, information-based searches increases the marginal value of land, but not enough to change this result qualitatively.<sup>46</sup>

Other studies focus on different aspects of bioprospecting problems but reach similar conclusions. Taking a somewhat different modeling approach, Barbier and Aylward conclude it is unlikely that revenues from bioprospecting alone will adequately compensate for the opportunity costs of habitat protection.<sup>47</sup> They suggest, however, that countries could be adequately compensated for investments to develop taxonomic information. Their conclusions appear consistent with ICBG projects that have funded such taxonomic information collection but have yet to yield significant royalty payments to finance large-scale conservation efforts.<sup>48</sup> Barrett and Lybbert emphasize the difficulties of transferring bioprospecting gains to the poor in tropical countries, who are making land-clearing decisions.<sup>49</sup> Frisvold and Condon emphasize that the opportunity costs of conservation are products of landholding inequality, poverty, tenurial insecurity, and government policies that encourage habitat conversion.<sup>50</sup> Rather than focus on the absolute value of bioprospecting gains, they argue that opportunity costs are large relative to potential bioprospecting gains and growing significantly over time.

Yet another approach, taken by Polasky and Solow, developed a more general model of the search process.<sup>51</sup> They point out that, contrary to the Simpson

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44. Christopher Costello & Michael Ward, *Search, Bioprospecting, and Biodiversity Conservation*, 52 J. ENVTL. ECON. & MGMT. 615, 616–25. (2006).

45. *Id.* at 625.

46. *See* Costello & Ward, *supra* note 44, at 623–25. The mean estimate of the marginal value of the most biodiverse area was \$1.23/hectare with random search. Assuming a more information-based search process raised this value to \$14/hectare, which is still low. *See id.*

47. Edward B. Barbier & Bruce A. Aylward, *Capturing the Pharmaceutical Value of Biodiversity in a Developing Country*, 8 ENVTL. & RES. ECON. 157, 173 (1996).

48. Day-Rubenstein & Frisvold, *supra* note 12, at 215; Rosenthal, *supra* note 25, at 282–87.

49. Christopher B. Barrett & Travis J. Lybbert, *Is Bioprospecting a Viable Strategy for Conserving Tropical Ecosystems?*, 34 ECOLOGICAL ECON. 293, 294 (2000).

50. Frisvold & Condon, *supra* note 14, at 5–6.

51. *See* Steven Polasky & Andrew R. Solow, *On the Value of a Collection of Species*, 29 J. ENVTL. ECON. & MGMT. 298 (1995).

et al. and the Rausser and Small models, species sharing a beneficial trait may not be perfect substitutes, so search will not necessarily terminate upon the discovery of the first species with the trait (the one-hit assumption).<sup>52</sup> In a “multiple-hit” model with imperfect substitution, they present an illustrative example where the value of the marginal species can reach three times higher than under a single-hit specification.<sup>53</sup> They also note that if a species with a beneficial trait is discovered, then close relatives will have a higher conditional probability of also being beneficial. So, subsequent searches may focus on those close relatives. Indeed, as shown below, this kind of search occurred in the case of taxol. They do not, however, formally explore the implications of this observation.

Economic studies of bioprospecting contracts, in sum, offer rather pessimistic assessments of the potential of these contracts to provide significant incentives for biodiversity conservation. Study results, however, are sensitive to assumptions about underlying relationships (for which there is often limited data) and simplifying assumptions used to make numerical economic models tractable.

### III. AIMS AND SCOPE OF STUDY

All of these economic studies are *ex ante* assessments based on numerical simulations with highly uncertain parameter values or on conjectures about the effects of different factors on the marginal benefits and costs of habitat protection. This Article adopts a different approach. It uses a case study of the blockbuster cancer drug taxol to ask what happens when a discovery is actually made.

Taxol was originally derived from the Pacific yew tree (*Taxus brevifolia*) found in old growth forests of the Pacific Northwest.<sup>54</sup> Today, the main sources of taxol are species of Asian yew, listed by the World Wildlife Fund as among the ten species most threatened by illegal trade.<sup>55</sup> Taxol’s discovery was the result of a twenty-year collection and screening program carried out by the U.S. Department of Agriculture (“USDA”) and the National Cancer Institute (“NCI”). The drug was brought to market in 1993 by the pharmaceutical corporation Bristol-Myers Squibb (“BMS”), a result of a Cooperative Research and Development Agreement (“CRADA”) between NCI and BMS. Used to treat late-stage ovarian and breast cancer as well as AIDS-induced Kaposi’s sarcoma, taxol became the number one selling anti-cancer drug in the world, garnering \$9 billion in sales for BMS from 1993 to 2002.<sup>56</sup> The development of taxol touched off a number of controversies over resource management, drug pricing, and trade in endangered species.

We use the case study to draw some policy lessons. First, drug search, discovery, and development differ in important ways from typical theoretical

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52. *Id.* at 299–300.

53. *Id.* at 301–02.

54. Croom, *supra* note 3, at 42.

55. Press Release, World Wildlife Fund, WWF Announces “10 Most Wanted Species” (Sept. 8, 2004), *available at* <http://worldwildlife.org/news/displayPR.cfm?prID=141>.

56. U.S. GEN. ACCOUNTING OFFICE, REPORT TO THE HONORABLE RON WYDEN, U.S. SENATE, GAO-03-829, TECHNOLOGY TRANSFER: NIH-PRIVATE SECTOR PARTNERSHIP IN THE DEVELOPMENT OF TAXOL 1, 1–5 (June 2003).

characterizations of bioprospecting literature. Compounds are not simply a “hit” or “miss” but have multiple attributes, some desirable (e.g., chemical activity against tumors) and others not (e.g., toxicity to patients). As Polasky and Solow note, achieving a “hit” or “miss” does not necessarily terminate a drug search.<sup>57</sup> Rather than rendering similar species redundant, a finding that a compound has medical activity can actually increase the value of similar species. For example, a compound with desirable chemical activity but harsh side effects may touch off a search for compounds with the same activity but with fewer negative side effects. Also, determining whether a compound holds commercial promise can take several years. Further, as screening methods evolve over time, so can assessments of a compound’s marketability—taxol bounced from being “hit” to “dead end” status a number of times before it was successfully marketed.

Second, the experience of taxol suggests that, contrary to hopes of conservationists, bioprospecting contracts are not likely to create strong incentives for *in situ* conservation and sustainable harvesting, which presumes continued harvesting of resources from their source. Harvesting Pacific yew bark from old growth forests in the Pacific Northwest proved problematic, and other alternatives of producing taxol, such as *ex situ* cultivation of plants on a mass scale and chemical semi-synthesis, soon proved more attractive options.

Third, and most importantly, a discovery can replace one biodiversity threat for another. Swanson notes species face two main extinction threats.<sup>58</sup> One is habitat conversion: species are lost because they are undervalued and their habitat is put to some other economic use. Originally, the Pacific yew had little commercial value and was burned as a “trash tree” after clear-cutting harvests of Douglas fir. As we will see, even after yew bark’s value as a cancer-fighting compound was established, it required an act of Congress (the “Pacific Yew Act”) to end this practice on federal lands.<sup>59</sup> The second threat comes from over-harvesting.<sup>60</sup> Here, the resource is valued, but property rights over the resource or its habitat lack clear definition. Pacific yew’s new-found value touched off incidents of poaching and a shift to harvesting on private lands with less regulatory oversight and cost. Ultimately, the main source of taxol has become Asian yews, harvested under less well-defined property rights regimes. Asian yews are now listed as Appendix II species under the Convention on International Trade in Endangered Species of Wild Fauna and Flora (“CITES”).<sup>61</sup> The case of taxol shows that bioprospecting, by creating a valuable product with open access sources

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57. Polasky & Solow, *supra* note 51, at 298.

58. Timothy M. Swanson, *The Economics of Extinction Revisited and Revised: A Generalised Framework for the Analysis of the Problems of Endangered Species and Biodiversity Losses*, 46 OXFORD ECON. PAPERS 800, 809–21 (1994).

59. Pub. L. No. 102-335, 106 Stat. 859 (1992).

60. Swanson, *supra* note 58, at 810.

61. Convention on International Trade in Endangered Species of Wild Fauna and Flora, Mar. 3, 1973, 27 U.S.T. 1087 [hereinafter CITES]. Species listed under Appendix II are not necessarily threatened with extinction, but it is determined that their trade must be controlled to avoid use which is incompatible with their survival. See GINETTE HEMLEY, INTERNATIONAL WILDLIFE TRADE: A CITES SOURCEBOOK 1–8 (1994).

of supply, can have unintended negative implications for biodiversity conservation.

The taxol case study also illustrates the importance of property rights at different stages of the search, development, and production process. These include property rights governing land (habitat), species, individual molecules, and finally ownership of the final consumer product (the drug). Property rights varied across these different assets over time and place, variably influencing the incentives of different actors in taxol development.

#### IV. DISCOVERY AND SCREENING OF TAXOL

Our story begins in 1958, when the NCI initiated a natural products program that over the course of over twenty years would screen 35,000 plants for anticancer activity.<sup>62</sup> Table 1 provides a chronology of taxol discovery, testing, and commercial development. As part of its natural products efforts, NCI began informal relationships with the USDA, an agency with experience in plant collection. The two agencies developed a formal agreement in 1960 that lasted until 1981.<sup>63</sup> In 1962, pursuant to this agreement, USDA botanist Arthur Barclay collected samples of Pacific yew (*Taxus brevifolia*) from Gifford Pinchot National Forest in Washington.<sup>64</sup>

**Table 1. Chronology of events in taxol development**

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|      |   |
|------|---|
| 1958 | The NCI initiates the Natural Products Program.   |
| 1960 | NCI enters into inter-agency agreement with USDA to collect plants for cancer screening.                                |
| 1962 | Pacific yew ( <i>Taxus brevifolia</i> ) samples taken from Washington's Gifford Pinchot National Forest.                |
| 1964 | Research Triangle Institute researchers find extract from Pacific yew bark has antitumor activity.                      |
| 1966 | First isolation of taxol molecule.  |
| 1967 | Report of taxol isolation to American Chemical Society annual meeting.  |
| 1971 | Taxol's chemical structure published (placing molecule and its name in the public domain).                              |
| 1979 | Researchers at Albert Einstein College of Medicine publish <i>Nature</i> article on taxol's unique mechanism of action. |
| 1983 | Investigational New Drug Application filed for taxol.   |
| 1984 | Phase I clinical trials begin.  |
| 1985 | Taxol approved for Phase II trials.   |
| 1986 | Clinical trial progress slowed by scarcity of taxol.<br>Federal Technology Transfer Act enacted.                        |
| 1987 | NCI contracts Hauser Chemical to collect Pacific yew bark and to  |

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62. Detailed histories of taxol's discovery and development are provided in TAXOL®: SCIENCE AND APPLICATIONS, *supra* note 3; JORDAN GOODMAN & VIVIAN WALSH, THE STORY OF TAXOL: NATURE AND POLITICS IN THE PURSUIT OF AN ANTI-CANCER DRUG (2001).

63. Matthew Suffness & Monroe E. Wall, *Discovery and Development of Taxol*, in TAXOL®: SCIENCE AND APPLICATIONS, *supra* note 3, at 22.

64. GOODMAN & WALSH, *supra* note 62, at 50–51.

manufacture taxol.

- 1988 French research team publishes results of taxol semi-synthesis using needles for European yew.
- 1989 Johns Hopkins researchers publish results of taxol's activity against ovarian cancer.  
In a *Federal Register* notice, NCI requests bids from companies to develop taxol under a Cooperative Research and Development Agreement; Bristol-Myers Squibb ("BMS"), Rhone-Poulenc, and two other companies apply.  
Researchers at Florida State University patent method of producing taxol by semi-synthesis.
- 1990 BMS and Florida State sign licensing agreement for use of semi-synthesis. Environmental groups petition Fish and Wildlife Service (FWS) to have the Pacific yew listed as a threatened species.
- 1991 NCI and BMS sign CRADA to commercially develop taxol. FWS rules against listing Pacific yew as threatened. M.D. Anderson researchers publish results of taxol's activity against breast cancer.
- 1992 Pacific Yew Act enacted. U.S. Patent and Trademark Office approves BMS's application to trademark the name Taxol® with generic name given as paclitaxel. In December, FDA approves use of taxol for metastatic ovarian cancer. NCI enters into CRADA with Rhone-Poulenc to develop taxotere.
- 1993 Commercial sale of taxol begins.
- 1994 FDA approves use of taxol for metastatic ovarian cancer. FDA approves production of taxol via semi-synthesis using patented Florida State process.
- 1995 Himalayan yew listed in CITES Appendix II. Chemical extracts excluded from listing.
- 1996 FDA approves taxotere for treatment of breast cancer.
- 1997 FDA approves use of taxol for AIDS-related Kaposi's sarcoma. In July, drug manufacturers filed applications with FDA to sell generic versions of taxol. BMS files suit in a federal district court alleging violations of its most recent patents on methods to administer taxol. BMS granted an additional 30 months of marketing exclusivity.
- 1998 FDA approves taxotere for treatment of breast cancer and lung cancer.
- 1999 FDA approves taxotere for treatment of lung cancer. Taxol becomes the biggest selling cancer drug in history. Annual global sales reach \$1.4 billion.
- 2000 First generic versions of taxol marketed.
- 2002 29 states file suit against BMS in federal district court for colluding to delay entry of generic versions of taxol.
- 2003 Federal Trade Commission consent order settles charges that BMS engaged in unlawful acts to delay competition from generic versions of taxol and two other of its major drugs.
- 2004 Expanded list of Asian *taxus* varieties and chemical derivatives listed in CITES Appendix II.

2007 Asian yew varieties placed on World Wildlife Fund's "10 Most Wanted List" of species threatened by illegal trade.

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When searching within a given area, the USDA collection program prioritized plants where folkloric knowledge of a plant's activity existed. However, they did not systematically search for plants based on folkloric leads.<sup>65</sup> Indian tribes in the Pacific Northwest used Pacific yew to treat a wide range of ailments from bronchitis, to headaches, to stomach and lung problems.<sup>66</sup> In Europe, yew has long been associated with death and poison.<sup>67</sup> For the ancient Greeks, yew was sacred to Hecate, the goddess of the underworld. Yew also figures in the works of Shakespeare. Hamlet's uncle poisoned Hamlet's father using "cursed hebona," a yew extract.<sup>68</sup> In Macbeth, the three witches threw "slips of yew slivered in the moon's eclipse" into their cauldron.<sup>69</sup> More recently, the wand of Lord Voldemort, the arch-villain of the *Harry Potter* series, was made of yew.<sup>70</sup>

Despite this folkloric knowledge, Pacific yew was not afforded any particular prominence in the initial sampling and screening. Samples of Pacific yew were shipped back to Bethesda, Maryland. Extracts were found to kill tumor cells in initial screens. The first pure sample of a complex molecule derived from Pacific yew was isolated in 1966 by Monroe Wall of the Research Triangle Institute.<sup>71</sup> In 1967, Wall named the compound taxol (a concatenation of *taxus* and alcohol) and presented results of the compound's structure at the 1967 meetings of the American Chemical Society.<sup>72</sup> Wall and associates published the description of taxol's isolation, structure, and anti-tumor properties in the *Journal of the American Chemical Society* in 1971.<sup>73</sup> This publication placed the molecule firmly in the public domain and, at the time, apparently precluded its patenting.

The prospects for taxol's commercial development were doubtful at several stages.<sup>74</sup> Under different screens, taxol showed varying activity against different tumors. Screening continued from 1967 to 1982. At a number of points it looked like taxol would be dropped from further consideration. Researchers at NCI were keenly aware of opportunity costs. A decision to pursue one lead came at the expense of pursuing others. For example, solubility is needed to be able to administer chemotherapies intravenously; taxol was virtually insoluble in water (and other solutions researchers tried). NCI researchers considered dropping taxol. Competing compounds showed equal or better anti-tumor activity but without the

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65. Suffness & Wall, *supra* note 63, at 4–5.

66. Croom, *supra* note 3, at 42.

67. Harold R. Hartzell, Jr., *Yew and Us: A Brief History of the Yew Tree*, in TAXOL®: SCIENCE AND APPLICATIONS, *supra* note 3, at 27–34.

68. WILLIAM SHAKESPEARE, HAMLET act 1, sc. 5.

69. WILLIAM SHAKESPEARE, MACBETH act 4, sc. 1.

70. J.K. ROWLING, HARRY POTTER AND THE SORCERER'S STONE (1998).

71. GOODMAN & WALSH, *supra* note 62, at 55–56.

72. *Id.* at 56.

73. Mansukhlal C. Wani et al., *Plant antitumor agents. VI. Isolation and structure of taxol, a novel antileukemic and antitumor agent from Taxus brevifolia*, 93 J. AM. CHEM. SOC. 2325, 2325–27 (1971).

74. GOODMAN & WALSH, *supra* note 62 (summarizing taxol's development).

solubility problem.<sup>75</sup> Then, it was discovered that taxol could be dissolved in a castor-oil derived compound Cremophor EL.<sup>76</sup> In 1979, researchers at the Albert Einstein College of Medicine published an article in *Nature* identifying that taxol had a unique mechanism of action for stopping tumor growth.<sup>77</sup> The fact that taxol attacked tumors in a novel way worked in its favor. The taxol-Cremophor EL combination was found to be active in tumor screens in 1980, but toxicology studies completed in 1982 suggested that there may be significant negative side effects.<sup>78</sup>

This process illustrates that screening is not a simple matter of finding one-off “hits” but rather that searches are lengthy, interdependent, and sensitive to technological change in the screening process itself. Also, promise was not and could not be measured as a one-dimensional “hit” but depended on multiple attributes of the compound.

In 1981, NCI discontinued its joint collection and screening program with the USDA.<sup>79</sup> From 1960 to 1981, the program screened more than 130,000 plant and animal extracts.<sup>80</sup> Of all the compounds screened and dozens that looked promising initially, only taxol moved to the stage of testing on humans, and this occurred two decades after its initial screening.<sup>81</sup>

NCI filed an Investigational New Drug Application for taxol with the Food and Drug Administration in 1983, and Phase I clinical trials began in 1984.<sup>82</sup> Phase I trials are used to determine a drug’s safety and dosage. In these trials, a number of patients had hypersensitivity reactions that included anaphylactic shock and two deaths.<sup>83</sup> It looked again like taxol would be dropped. However, it was found that the hypersensitivity reactions could be limited by slowing the rate of infusion, pre-medication, and excluding patients with cardiac risk factors, illustrating once again the complexities of the screening process.<sup>84</sup>

## V. TAXOL SUPPLY PROBLEMS

Even at the early stages of taxol screening, it was apparent to researchers at NCI that developing adequate supplies of taxol could be a problem. First, because Pacific yews—taxol’s source—had little economic value, little was known about them. They were treated as “trash trees,” burnt on slash piles from clear-cut harvesting of Douglas fir or occasionally harvested to make fence posts. It was known that they grew in the understory of old growth forests throughout the

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75. Frank Stephenson, *A Tale of Taxol*, 12 RES. IN REVIEW 18–19 (2002).

76. Stephenson, *supra* note 75, at 19–20; Suffness & Wall, *supra* note 63, at 13–14.

77. Peter B. Schiff et al., *Promotion of microtubule assembly in vitro by taxol*, 277 NATURE 665, 665–67 (1979).

78. The most severe side effects were hypersensitivity reactions that included anaphylactic shock and two deaths. Some Phase I clinical trials were ceased because of these extreme reactions. See Suffness & Wall, *supra* note 63, at 13–18.

79. Suffness & Wall, *supra* note 63, at 4.

80. Stephenson, *supra* note 76, at 20–21.

81. *Id.* at 21.

82. GOODMAN & WALSH, *supra* note 62.

83. Suffness & Wall, *supra* note 63 at 17–18.

84. GOODMAN & WALSH, *supra* note 62.

Pacific Northwest, but their numbers and distribution were undocumented. Most yews were believed to be on federal lands administered by the U.S. Forest Service and the Bureau of Land Management.<sup>85</sup> This meant that these agencies and laws governing harvesting on federal lands would come into play as Pacific yew was harvested.

Second, while bark yielded orders of magnitude more taxol than other parts of the tree, substantial amounts of Pacific yew bark were needed to produce small amounts of taxol. Taking estimates from Croom, commercial-scale production of taxol required 13,000 to 16,000 pounds of dry bark to produce 1 kg of taxol; the treatment regimen was 2 g of taxol per patient; and 3.33 to 5 pounds of bark could be harvested per tree.<sup>86</sup> Harvesting bark necessitates killing the trees, implying that roughly six to nine trees would be needed per patient. More renewable sources, such as needles, yielded far less taxol than bark. In addition, NCI-funded studies found that taxol yield varied substantially across yew species. Research also found that taxol content varied greatly for Pacific yew across different collection sites.<sup>87</sup>

Third, yews are extremely slow-growing trees. In one Forest Service survey, it took 25 years for trees to reach a diameter of 2.5 cm (1 inch) and 100 years to reach 15.2 cm (6 inches).<sup>88</sup> Thus, as a source of taxol, Pacific yew bark was renewable in only the very long run.

Finally, studies found that more common species of yew had problems of their own. As briefly noted above, common, ornamental yew varieties, such as the European yew (*Taxus baccata*) and Japanese yew (*Taxus cuspidata*) yielded significantly lower amounts of taxol than Pacific yew did. Moreover, there were indications that compounds derived from these varieties might be more cardiotoxic than compounds from Pacific yew.<sup>89</sup>

In 1985 Phase II clinical trials, used to establish drug efficacy, were approved. Trials began for treatment of ovarian cancer, melanoma, and renal cancer.<sup>90</sup> Taxol showed the greatest effectiveness against ovarian cancer.<sup>91</sup> While taxol was showing promise in hospitals, its limited supply was threatening the continuation of clinical trials. Contractors hired by NCI to harvest yew bark had difficulty delivering agreed-upon quantities of bark on time. Several other clinical trials were put on hold, in part because sufficient supplies of taxol simply were not available.<sup>92</sup>

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85. Croom, *supra* note 3, at 41, 44.

86. *Id.* at 43–45.

87. *Id.* at 51–55.

88. Charles L. Bolsinger & Annabelle E. Jaramillo, *Taxus brevifolia* Nutt., *Pacific Yew*, in *SILVICS OF NORTH AMERICA* 573 (Russell M. Burns & Barbara H. Honkala eds., 1990).

89. Cardiotoxic literally means “poisonous to the heart.” A substance is cardiotoxic if it has poisonous or deleterious effect on the functioning of the heart. For more discussion of toxicity of taxol, see Suffness & Wall, *supra* note 47, at 7–8.

90. GOODMAN & WALSH, *supra* note 62, at 119.

91. *Id.*

92. *Id.* at 118–19.



In 1988, researchers at Johns Hopkins University found that patients with refractory ovarian cancer had relatively high response rates to taxol, publishing their findings in 1989.<sup>93</sup> These responses were in women who had failed to respond to earlier chemotherapy treatments. This discovery, although exciting from a health perspective, brought the supply problem into sharp focus. Contract harvesters were having difficulty supplying 60,000 pounds of bark per year.<sup>94</sup> Yet, over 60,000 women die of ovarian cancer per year. Producing enough taxol to treat all these women would require over 1.7 million pounds of bark!<sup>95</sup>

NCI administrators began to look elsewhere for sources of taxol and for a private firm to handle commercial scale production. Officials had already approached the timber company Weyerhaeuser about the possibility of mass propagation of Pacific yew seedlings.<sup>96</sup> Taxol soon became "possibly the number one target of synthetic organic chemists."<sup>97</sup> A Stanford University research group partially synthesized the taxol molecule with material derived from pine trees.<sup>98</sup> While NCI funded some of this research, NCI scientists remained skeptical about producing taxol via total synthesis. Achieving synthesis in a laboratory and establishing economical commercial-scale production are very different processes, and at that time, only about four percent of natural product medicines were commercially produced by total synthesis.<sup>99</sup>

In 1988, a French research team succeeded in producing taxol via semi-synthesis, using needles of the European yew as a source to construct the main part of the molecule and then using synthetic methods to attach remaining parts.<sup>100</sup> This approach had two advantages. It used needles, which could be harvested renewably without killing trees, and it relied on the common European yew. The yield of taxol, however, was low, and NCI scientists did not pursue joint research with the French.<sup>101</sup>

In 1989 chemist Robert Holton of Florida State University developed a new method of producing taxol via semi-synthesis that produced double the yield of the French process.<sup>102</sup> Florida State University patented this method of producing taxol.<sup>103</sup> While the taxol molecule itself had been in the public domain, processes for making taxol could be patented. The following year, Florida State

93. William P. McGuire et al., *Taxol: a Unique Antineoplastic Agent with Significant Activity in Advanced Ovarian Epithelial Neoplasms*, 111 ANNALS OF INTERNAL MED., 273, 273-79 (1989).

94. GOODMAN & WALSH, *supra* note 62, at 121-25.

95. Croom, *supra* note 3, at 72.

96. GOODMAN & WALSH, *supra* note 62, at 128-29.

97. Jean-Noël Denis et al., *A Highly Efficient, Practical Approach to Natural Taxol*, 110 J. AM. CHEM. SOC'Y 5917, 5917-19 (1988).

98. Elaine Blume, *Taxol Synthesis in Perspective*, 84 J. NAT'L CANCER INST. 674 (1992).

99. Soejarto & Farnsworth, *supra* note 1, at 244.

100. Denis, *supra* note 73, at 5917-19.

101. GOODMAN & WALSH *supra* note 62, at 134-35.

102. Stephenson, *supra* note 75, at 23-24

103. *Id.* at 25-26.

University and the pharmaceutical company Bristol-Myers Squibb signed a licensing agreement for use of the semisynthesis process.<sup>104</sup>

## VI. CRADA WITH BRISTOL-MYERS SQUIBB

After 30 years of screening natural products, NCI finally had identified a marketable product. Yet, while NCI spearheaded the search and testing of anti-cancer treatments, they had neither the mission nor the resources to actually bring a product—once found—to market. Commercial taxol production would require forward linkages into pharmaceutical production and marketing and backward linkages into the forest products sector. According to the Federal Food Drug and Cosmetic Act, any party petitioning the FDA for a new drug application (“NDA”) process must provide FDA with “a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing, of such drug.”<sup>105</sup> NCI, as a cancer research agency, had no extract-processing facilities or final pharmaceutical production facilities of its own, making it very difficult to comply with the FDA requirements.

In 1980, Congress passed two pieces of legislation intended to encourage the commercialization of technologies developed with federal funding: the Stevenson-Wydler Technology Innovation Act of 1980<sup>106</sup> and the Bayh-Dole Act.<sup>107</sup> Stevenson-Wydler focused on inventions owned by the federal government, while Bayh-Dole Act focused on inventions created under federal contracts, grants, and cooperative research and development agreements. In 1986, the Federal Technology Transfer Act<sup>108</sup> amended Stevenson-Wydler. The amended act established guidelines to encourage commercialization of new technologies through licensing to private firms. It also authorized federal agencies to enter into Cooperative Research and Development Agreements with nonfederal entities (private firms, universities, etc.) to conduct research.<sup>109</sup>

By 1989, NCI officials saw mechanisms established under these new laws as a means of bringing taxol to market. On August 1, 1989, NCI solicited bids in the *Federal Register* for a Cooperative Research and Development Agreement (“CRADA”) to develop taxol commercially.<sup>110</sup> Only four firms bid: Bristol-Myers Squibb (“BMS”), the French chemical and pharmaceutical company Rhone-Poulenc (now Aventis), and two smaller biotechnology firms. BMS had the most experience with developing cancer drugs and with large-scale drug marketing in the United States. Further, some BMS officials were familiar with taxol through previous employment at NCI. BMS had already engaged in exploratory discussions with NCI and Weyerhaeuser over developing supplies of taxol. NIH reviewers deemed BMS the strongest applicant, and NCI signed a CRADA with BMS in 1991 to obtain FDA approval to commercially develop taxol.

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104. *Id.*

105. 21 U.S.C. § 355(b)(1)(D) (2000).

106. Pub. L. No. 96-480, 94 Stat. 2311.

107. Pub. L. No. 96-517, § 6(a), 94 Stat. 3015 (1980).

108. Pub. L. No. 99-502, 100 Stat. 1785 (1986).

109. *Id.*

110. 54 Fed. Reg. 31,733 (August 1, 1989).

Provisions of the CRADA included the following: (i) A committee of officers from both NCI and Bristol would review clinical trials and share research results; (ii) NCI would provide its own raw clinical trial data exclusively to BMS; (iii) NCI would “urge” outside researchers it funded at universities and hospitals to cooperate with BMS; (iv) NCI would work exclusively with BMS to develop and market taxol; (v) in exchange, BMS would supply NCI with taxol for clinical trials and other research, collect clinical trial data, and fund specific studies.<sup>111</sup> It was believed at the time that because taxol could not be patented, other measures would be necessary to provide BMS with enough exclusivity to profitably market the drug.

The CRADA specified Bristol’s estimate of funds and personnel necessary to develop taxol as well as the expected date for a New Drug Application.<sup>112</sup> Initially based on a “model” CRADA used by National Institute of Health agencies, the taxol development CRADA included a “reasonable price clause.” The clause stated that there should be “a reasonable relationship between the pricing of a licensed product, the public investment in that product, and the health and safety needs of the public.”<sup>113</sup> The original language also noted that evidence to justify pricing may be required. The final version of the CRADA signed in 1991, however, excluded the reasonable price clause at the insistence of BMS.<sup>114</sup>

In June of 1991, the NIH, USDA, and the Department of Interior signed a Memorandum of Understanding (“MOU”) regarding harvesting of Pacific yew for taxol production on lands administered by USDA (“Forest Service”) and Interior (Bureau of Land Management (“BLM”)).<sup>115</sup> The MOU effectively granted BMS exclusive access to yew bark on federal lands and designated Hauser Chemical Research (a contractee with BMS) as the sole recognized supplier of yew bark and processor of bark into taxol.<sup>116</sup> So, even though BMS did not hold a patent on taxol itself, it controlled proprietary medical data needed for FDA approval and exclusive rights to harvest bark on federal lands.

The Forest Service and BLM were criticized for providing BMS with exclusive access to Pacific yew trees and not charging BMS a sufficiently large price per pound for harvesting yew bark.<sup>117</sup> However, *not* charging for yew bark may have been, in effect, a way to address a potential double marginalization

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111. Kelly A. Day & George B. Frisvold, *Medical Research and Genetics Resources Management: the Case of Taxol*, CONTEMP. POL’Y ISSUES, July 1993, at 1, 1–11.

112. *Id.*

113. U.S. GEN. ACCOUNTING OFFICE, *supra* note 56, at 8.

114. *Id.*

115. GOODMAN & WALSH, *supra* note 62, at 168.

116. Day & Frisvold, *supra* note 111, at 6; GOODMAN & WALSH, *supra* note 62, at 168.

117. See, e.g., Daniel Newman, *The Great Taxol Giveaway*, MULTINATIONAL MONITOR, May 1992, at 17; Ralph Nader & James Love, *Looting the Medicine Chest: How Bristol-Myers Squibb Made Off With the Public’s Cancer Research*, PROGRESSIVE, Feb. 1993, at 26 (1993).

problem.<sup>118</sup> It is not clear how a policy of high mark-up pricing by the Forest Service or BLM would have improved overall welfare or that of cancer patients.

Critics also argued that giving BMS and Hauser monopoly control over yew bark collection on Federal lands led to wasteful harvesting. Harvesters partially stripped easy-to-reach parts of trees, leaving remaining bark unharvested. Some contended that collectors harvested only bark they could easily gather and that allowing greater competition in harvesting would increase the amount of bark harvested per tree.<sup>119</sup>

This argument is misplaced for two reasons. First, companies generally extract resources more slowly under monopoly than under competition.<sup>120</sup> Dasgupta and Heal quote the adage, "the monopolist is the conservationist's best friend."<sup>121</sup> Second, the manner of bark collection resulted from the nature of piece-rate contracts rather than from the BMS monopoly. Yew bark collection was subcontracted and carried out by local harvesters paid piece rate. Piece rates reward getting the most bark per unit of labor effort, not the most bark per tree.<sup>122</sup> Allowing more firms to become involved with harvesting would not have changed this underlying incentive. More trees would have been stripped of bark (and killed), but there is no reason to expect that bark would have been stripped more thoroughly from each tree, leaving the ultimate conservation equation unchanged.

BMS and NCI remained active in the search for renewable alternatives to Pacific yew bark.<sup>123</sup> They collaborated with parties to examine *Taxus* species in Canada, Mexico, Europe, and China. In 1991, NCI awarded a \$1.27 million grant to a research consortium consisting of USDA's Agricultural Research Service, Cornell University, Colorado State University, Hauser Chemical Company, and the biotechnology firm Phytion Catalytic, Inc.<sup>124</sup> The consortium intended to produce taxol via plant tissue culture. The USDA originally discovered and held

118. Discussion of double marginalization, the exercise of market power at successive vertical layers in the supply chain, dates back to A.P. Lerner, *The Concept of Monopoly and the Measurement of Monopoly Power*, 1 REV. ECON. STUD. 157 (1934). This problem arises when more than one firm in the supply chain faces a downward sloping demand curve and has the incentive to mark up the product's price above its marginal cost. The sequence of mark-ups leads to a higher retail price and lower combined profit for the supply chain than would arise if the firms were vertically integrated. Consequently, consumer surplus and industry profits rise when firms in the same supply chain merge.

119. Timothy Egan, *Trees that Yield a Drug for Cancer Are Wasted*, N.Y. TIMES, Jan. 29, 1992, at A1.

120. Scott Gordon, *Economics and the Conservation Question*, 1 J.L. ECON. 110, 117-18 (1958).

121. P.S. DASGUPTA & G. M. HEAL, *ECONOMIC THEORY AND EXHAUSTIBLE RESOURCES* 323-28 (1979). Theoretically, resource depletion can occur more rapidly under monopoly than under competition. See *id.*; see also ANTHONY C. FISHER, *RESOURCE AND ENVIRONMENTAL ECONOMICS* (1981). However, this may require that the product find many new users as its price got very low. This seems unlikely because there is a limited number of people with late-stage cancers.

122. One cannot assume that completely stripping each tree of bark is economically efficient, given positive harvesting costs and costs of delay to cancer patients.

123. Day & Frisvold, *supra* note 111, at 4.

124. *Id.*

the patent for production of taxol in tissue culture. As noted earlier, BMS maintained a licensing agreement with Florida State University to produce taxol via semisynthesis. Weyerhaeuser, funded by BMS, scaled up commercial scale nursery plantation production from 0.5 million rooted cuttings in 1991 to 10 million in 1993.<sup>125</sup> A research group called “the Alliance for Taxol” included scientists from Ohio State University, the University of Mississippi, the USDA, and large private nurseries. The Alliance worked on developing taxol from leaves of ornamental yew varieties.<sup>126</sup> For the time being, however, production of taxol using Pacific yew bark was the only method approved by FDA for clinical trials. With Phase III clinical trials beginning, taxol from Pacific yew bark would have to serve as the supply.<sup>127</sup>

## VII. CONTROVERSIES OVER PACIFIC YEW HARVESTING

With the Pacific yew the only viable source of taxol, commercial-scale harvesting of Pacific yew bark on federal lands quickly became controversial as part of a larger debate over protection of old-growth forests and endangered species in the Pacific Northwest. Advocates and opponents of the Endangered Species Act each used taxol and the plight of cancer patients to bolster their arguments.<sup>128</sup> It eventually required an act of Congress—the Pacific Yew Act—to establish protocols for bark harvesting.<sup>129</sup>

The Pacific Northwest was already embroiled in an intense political debate over timber harvesting and endangered species protection in old-growth forests. In 1987, environmental groups petitioned the Fish and Wildlife Service (FWS) to list the Northern Spotted Owl, a denizen of those forests, as an endangered species. In April 1989 the FWS finally found that the owl was a threatened species and posted its finding in the June 23, 1989 *Federal Register*.<sup>130</sup> Environmental groups successfully halted timber sales on Forest Service and BLM lands that were Spotted Owl habitat.<sup>131</sup> As timber sales began to decline in the Pacific Northwest for the first time in 40 years, intense public debates over “jobs vs. owls” ensued.

Some environmentalists saw the discovery of taxol as a vindication of the Endangered Species Act. The preservation of Pacific yew, incidentally destroyed as a trash tree during Douglas fir harvesting, was aided by the protection of habitat it shared with the Spotted Owl.<sup>132</sup> Taxol reframed the ESA debate from one of jobs vs. owls to one of cancer patients vs. timber sales.

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125. Croom, *supra* note 3, at 60.

126. *Id.* at 61–62.

127. Phase III trials are conducted on large numbers of patients to assess how a new drug performs (not just absolutely) but relative to existing standard methods of treatment. DEP'T OF HEALTH & HUMAN SERVS., THE CDER HANDBOOK 8 (1998).

128. See, e.g., Jeffrey Weiss, *Rival Causes Yearn to Hug Yew Tree's Cancer Curing Potential Has Environmentalists and Timbermen Using It to Prop Up their Arguments*, TORONTO STAR, Sept. 7, 1991, at 6.

129. Pub. L. No. 102-335, 106 Stat. 859 (1992).

130. 54 Fed. Reg. 26,666 (June 23, 1989).

131. GOODMAN & WALSH, *supra* note 62 at 196.

132. *Id.* at 195–96, 211–15.

In September 1990, environmental groups along with cancer researchers petitioned FWS to list the Pacific yew as a threatened species under the Endangered Species Act based on species depletion rates and on the need to preserve the yew as a taxol source.<sup>133</sup> The petition argued that forest clear-cutting had led to destruction of much Pacific yew habitat and therefore called into question timber harvesting and sales in broader terms.

In August 1991, FWS refused the listing because of insufficient scientific information about logging's impact on the yew population's long-term viability.<sup>134</sup> In 1990, the Forest Service, based on satellite photography and other indirect measures, had estimated that 130 million yew trees were growing on federal land.<sup>135</sup> The FWS refusal cited this early population estimate. The Forest Service subsequently revised their estimate downwards to about 20 million yews.<sup>136</sup> Because the Endangered Species Act does not protect species as medical research resources, FWS did not consider the impact of taxol demand on the Pacific yew population.<sup>137</sup> Consequently, FWS based depletion estimates on the incidental destruction of yews during commercial logging rather than on yew harvest for taxol development. Furthermore, FWS did not regard the loss of mature trees, needed for cancer treatment, as a threat to species survival, arguing that smaller trees would be untouched.<sup>138</sup>

Environmental groups then shifted attention to how current timber harvesting practices affected collection and utilization of yew bark. Again, clear-cutting practices in general were criticized. In December of 1991, the Environmental Defense Fund and the Wilderness Society petitioned USDA and Interior to require pre-harvest yew bark collection.<sup>139</sup> The petition cited a Forest Service memo stating that between 60-75% of bark was wasted if harvest did not occur prior to logging. The Forest Service had urged, but not required, the harvest of small yew trees, and BLM required no yew harvesting prior to clear-cutting. The Oregon Natural Resources Council also attempted to block timber sales until the Forest Service and BLM issued guidelines for harvesting yew trees and completing inventories and long-term management plans for the species.<sup>140</sup>

These actions created some unintended public-relations problems for environmental groups. News stories and editorials began to frame the debate in

133. Env'tl. Def. Fund, Petition to the Secretary of Interior for listing the Pacific yew as a threatened species (Sept. 19, 1990).

134. Endangered and Threatened Wildlife and Plants: Notice of 90-day Finding on Petition To List *Taxus brevifolia* (Pacific Yew) as Threatened, 56 Fed. Reg. 40,854 (August 16, 1991) [hereinafter Notice on Petition To List Pacific Yew as Threatened].

135. *Id.*

136. Day & Frisvold, *supra* note 111, at 5.

137. *Id.* at 6-7.

138. Notice on Petition To List Pacific Yew as Threatened, *supra* note 134.

139. Env'tl. Def. Fund, *supra* note 133.

140. Richard Cockle, *Yew Stand Stirs Challenge to Timber Sale*, OREGONIAN, Sept. 5, 1991, at C02; Kathleen Monje, *Forest's Yew Tree Policy Lax, Appeal Claims*, OREGONIAN, July 3, 1992, at C02; Dana Tims, *Pacific Yew at Center of Timber Sales Appeal*, OREGONIAN, Feb. 27, 1991, at B05.

terms of owls and trees vs. cancer patients.<sup>141</sup> Some went so far as to argue that additional clear-cutting was the only way to provide sufficient taxol to cancer patients.<sup>142</sup>

Environmental groups countered that it was not the harvest of yew bark they opposed, but that bark was not being harvested either sustainably or thoroughly in areas already designated as clear-cutting areas.<sup>143</sup> In January of 1992, Forest Service crews reportedly continued to burn yew bark in routine fires of clear-cutting residue.<sup>144</sup> During March of 1992 in House Subcommittee on Regulation, Business Opportunities, and Energy hearings, BLM and Forest Service officials testified that yew harvesting would be required prior to commercial logging on federal land and subsequently issued directives to this effect.<sup>145</sup> A 1992 GAO report on constraints on obtaining yew bark supplies concluded that yew bark was often not harvested either prior to clear cutting or taken from slash piles on federal lands.<sup>146</sup> The report did not mention environmental restrictions, such as special protections for Spotted Owl nesting areas, as a constraint on harvesting.

In 1992, Congress passed the Pacific Yew Act.<sup>147</sup> The law gave the Secretaries of Agriculture and the Interior broad authority to limit illegal harvesting of yews on federal lands.<sup>148</sup> It required that an inventory of yews be taken, and it also provided for appropriate management guidelines to prevent wasting of Pacific yew bark.<sup>149</sup>

These problems with Pacific yew harvest highlight Croom's point that "currently there are no universally acceptable environmental harvesting guidelines of plants" for pharmaceutical development.<sup>150</sup> More specific yew harvesting guidelines were developed in *An Interim Guide to the Conservation and Management of Pacific Yew, The Pacific Yew Draft Environmental Impact*

141. Special restrictions were placed on harvesting yew bark near Spotted Owl nesting areas. Federal agencies encouraged harvesting in areas that had already been clear cut or were approved for clear-cut timber harvesting. In the former case, bark could be harvested from slash piles, while in the latter, yew bark harvest could proceed prior to clear-cut harvesting. For newspaper stories posing the problem as one of conflict between environmental protection and cancer patients, see for example William Safire, *To Hell with Yew?*, N.Y. TIMES, May 16, 1991, at A23; *I Am Endangered Too*, WASH. TIMES, Dec. 23, 1991, at E2; Sallie Tisdale, *Save a Life, Kill a Tree?*, N.Y. TIMES, Oct. 26, 1991, at 19.

142. See, e.g., William McGuire, *Ovarian Cancer vs. The Spotted Owl*, 15 MED. UPDATE 1, 1-2 (1991).

143. Wendell Wood, *Pacific Yew Harvesting Not Aimed at Protecting Trees over Long Run*, OREGONIAN, July 28, 1992, at B06; Carl Ross, *Yew Trees Needn't Fall to Make Cancer Drug: Halt Clear-Cutting*, N.Y. TIMES, Feb. 22, 1992, at 22.

144. Egan, *supra* note 91.

145. Day & Frisvold, *supra* note 85.

146. U.S. GEN. ACCOUNTING OFFICE, *CANCER TREATMENT: EFFORTS TO MORE FULLY UTILIZE THE PACIFIC YEW'S BARK*, T-RCED-92-36, 1-4 (1992).

147. Pub. L. No. 102-335, 106 Stat. 859 (1992).

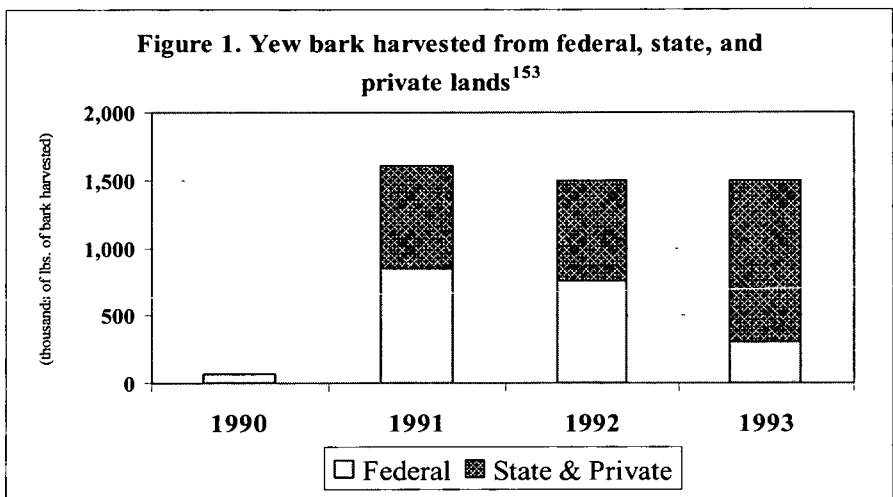
148. *Id.* § 5.

149. *Id.* § 7.

150. Croom, *supra* note 3, at 49.

*Statement, and the Pacific Yew, Final Environmental Impact Statement.*<sup>151</sup> Yet, it took an act of Congress and nearly a decade, after it was known that commercial scale harvesting of yew would proceed, for the development of workable harvesting guidelines.

While federal agencies were developing yew harvesting policies, there were a number of cases where private actors engaged in poaching. The Forest Service estimated that about 0.3 million pounds of wet bark were stolen, equivalent to about 0.15 million in dry bark.<sup>152</sup> Production also shifted from federal lands with greater regulatory costs to private lands. In 1990, all the legally harvested yew bark came from federal lands. As depicted in Figure 1, this fell to about half in 1991 and 1992 and down to 21% by 1993.<sup>153</sup>



### VIII. OUT OF THE WOODS AND INTO THE MARKET

In 1991 and 1992, two events spurred the end of Pacific yew harvesting in the Pacific Northwest. First, researchers at the M.D. Anderson Cancer Center published clinical trial results showing that patients responded well to taxol in

151. U.S. DEP'T OF AGRIC.-FOREST SERV. (USDA-FS), AN INTERIM GUIDE TO THE CONSERVATION AND MANAGEMENT OF PACIFIC YEW (March 1992); USDA-FS, THE PACIFIC YEW: DRAFT ENVIRONMENTAL IMPACT STATEMENT (Jan. 1993); USDA-FS, PACIFIC YEW: FINAL ENVIRONMENTAL IMPACT STATEMENT (Sept. 1993).

152. USDA-FS, THE PACIFIC YEW: DRAFT ENVIRONMENTAL IMPACT STATEMENT (Jan. 1993); see also Croom, *supra* note 3, at 46. A number of cases of poaching were carried in Pacific Northwest newspapers. Poachers were believed to either send supplies overseas or to supply BMS itself. See, e.g., Kathleen Monje, *\$6,000 Reward Offered after Bark Stripped from 56 Pacific Yews*, OREGONIAN, May 30, 1991, at B4; *Yew Bark Theft Reported*, OREGONIAN, Oct. 21, 1991, at A8; Eric Nalder, *Yew-Bark "Gold Rush" Prompts Sting*, SEATTLE TIMES, Oct. 20, 1991, at A15.

153. Croom, *supra* note 3, at 43-45.



treatment of metastatic breast cancer.<sup>154</sup> About 40,000 women in the United States die of breast cancer each year, and over 175,000 new cases are diagnosed per year.<sup>155</sup> As noted earlier, these results, while promising medically, again suggested that demand for taxol (and Pacific yew bark) would dramatically increase, compounding existing harvesting problems.

Next, in 1992, Robert Holton at Florida State University developed an even more efficient method of semisynthesizing taxol.<sup>156</sup> This method could use needles from Asian yew or European yew. Florida State again patented this invention and licensed it to BMS. This new method proved to be a cost-effective way to mass-produce taxol. In 1993, BMS announced that it planned to produce large amounts of taxol using the new semisynthesis process, that it would discontinue harvest of yew bark from federal lands, and that by 1995 all reliance on bark as a source of taxol would come to an end.<sup>157</sup>

In December 1992, the FDA approved taxol for treatment of ovarian cancer, and in 1993, BMS began to market it.<sup>158</sup> The FDA's approval of BMS's New Drug Application to market taxol for the treatment of ovarian cancer triggered a provision in federal law granting BMS five years of marketing exclusivity for taxol as a new chemical entity under the Drug Price Competition and Patent Term Restoration Act of 1984, more commonly known as the Hatch-Waxman Act.<sup>159</sup> The statute provides marketing protection for pharmaceuticals that cannot be patented by prohibiting introduction of a generic drug during the five-year exclusivity period.<sup>160</sup> Sales of taxol rose from \$162 million in 1993 to over \$1.5 billion in 2000 as taxol became the world's largest selling cancer drug.<sup>161</sup> Yet, this market success did not end taxol's ups and downs.

## IX. CONTROVERSY OVER TAXOL PRICING

BMS's pricing for taxol became one of the most controversial issues concerning the drug's development. The House Subcommittee on Regulation, Business Opportunities, and Energy held hearings on taxol pricing, which considered the fundamental tradeoff of intellectual property rights assignment between the desire to provide private incentives for technological innovation and the desire for widespread and early diffusion of innovation benefits.<sup>162</sup>

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154. F. Holmes et al., *Phase II Trial of Taxol, an Active drug in the Treatment of Metastatic Breast Cancer*, 83 J. NAT'L CANCER INST. 1797, 1805 (1991).

155. Am. Cancer Soc'y, *How Many Women Get Breast Cancer?* (Sept. 26, 2007), [http://www.cancer.org/docroot/CRI/content/CRI\\_2\\_2\\_1X\\_How\\_many\\_people\\_get\\_breast\\_cancer\\_5.asp?sitearea=](http://www.cancer.org/docroot/CRI/content/CRI_2_2_1X_How_many_people_get_breast_cancer_5.asp?sitearea=).

156. Stephenson, *supra* note 75, at 36–37.

157. Goodman & Walsh, *supra* note 62, at 235.

158. U.S. GEN. ACCOUNTING OFFICE, *supra* note 56, at 10.

159. U.S.C. § 355(b)-(c)(3)(D)(ii) (2000); *see also* H.R. Rep. No. 98-857, pt. 1, at 29 (1984), *reprinted in* 1984 U.S.C.C.A.N. 2647, 2647–48, 2662.

160. *Id.*

161. U.S. GEN. ACCOUNTING OFFICE, *supra* note 56, at 15–16.

162. T. Reynolds, *House Subcommittee Scrutinizes Taxol Agreement*, 83 J. NAT'L CANCER INST. 1049, 1134–35 (1991). BMS's exclusive access to Pacific yew trees on federal lands and taxol's ultimate patent protection secured private appropriability, which

In December 1992, BMS proposed a taxol price of about \$700 per treatment cycle.<sup>163</sup> Patients require an average of four treatment cycles. This cost was comparable to other ovarian cancer treatments. Bristol also announced that it would provide the drug free of charge to patients who could not afford it.<sup>164</sup>

The price Bristol charged for taxol continued to be controversial, given the substantial public funds invested in its development. Drug pricing controversies raised the question of what constitutes a fair rate of return to BMS's investment.<sup>165</sup> In 2003, the General Accounting Office ("GAO"), at the behest of Senator Ron Wyden of Oregon, issued a report critical of the NIH-BMS CRADA.<sup>166</sup> In 1997, other drug manufacturers filed applications with the FDA to sell generic versions of taxol.<sup>167</sup> BMS filed suit in a federal district court alleging violations of its most recent patents on methods to administer taxol. BMS was automatically granted an additional 30 months of marketing exclusivity as the case

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encourages innovation. On the other hand, concern existed about the inefficiency that such monopoly power might generate. Developing pharmaceuticals is a high-risk, high-payoff endeavor. The pharmaceutical industry claims that only one of 10,000 compounds studied ever proves useful and that only three of ten new medicines recoup their average cost. These risks and costs do not go unrewarded, however. Rates of return in the pharmaceutical industry are quite high, both absolutely and relative to other industries. Comparing the median rate of return to investors of Fortune 500 pharmaceutical companies and other Fortune 500 companies bears this out. The pharmaceutical industry's 1981-1991 annual rate of return was 25.3% compared to 15.5% for the Fortune 500 as a whole. Day & Frisvold, *supra* note 111, at 9.

163. Day & Frisvold, *supra* note 111, at 9.

164. *Id.*

165. Setting a specific price in the CRADA itself would have been difficult since a high degree of uncertainty existed about the ultimate cost of producing taxol. However, without directly setting a price, the government could have specified criteria that a pricing policy must meet. House Subcommittee hearings identified two mechanisms to limit taxol's market price. One mechanism is to provide for arbitration of price disputes directly in the CRADA. However, this approach places NCI in the business of monitoring and regulating firms' competitive behavior, an economic regulatory role outside its mission as a medical research agency and out of its area of expertise. A second mechanism was to encourage market competition through public research funding and cooperation strategies. A concrete example of such a strategy is NCI's CRADA with Rhone-Poulenc to develop Taxotere. Taxotere, based on the earlier semisynthesis research of French scientists, is derived from European yew needles and has a mechanism of action and molecular structure quite similar to taxol. See Day & Frisvold, *supra* note 111, at 9.

166. U.S. GEN. ACCOUNTING OFFICE, *supra* note 56. The GAO reported that NIH invested \$183 million on taxol research and development from 1977 to 1997. While BMS claimed to have spent \$1 billion on taxol research and development, and other costs associated with the CRADA, their gross sales of taxol totaled over \$9 billion from 1993 to 2002. *Id.* at 4. NIH received royalties from a licensing agreement with BMS at a rate of 0.5% and received only \$35 million through 2002. In contrast, Florida State University's agreement yielded a royalty rate of 4.2%. Florida State received \$28 million in royalties in 1996 alone and over \$200 million through to 2000. The GAO found that the federal government paid for investments in taxol's initial development and then became a major payer for taxol, through Medicare payments for taxol, which totaled \$687 million from 1994 to 1999. *Id.* at 4.

167. *Id.* at 10.

was reviewed.<sup>168</sup> In 2002, 29 states filed suit against BMS in federal district court charging it colluded with other firms to delay entry of generic versions of taxol.<sup>169</sup> In 2003, the Federal Trade Commission released a consent order to settle charges that BMS engaged in unlawful acts to delay competition from generic versions of taxol and two of its other major drugs.<sup>170</sup>

The consent order—and the events that led up to it—raise questions about the appropriateness of placing health agencies—namely NCI and FDA—in charge of key aspects of what are essentially economic policies: product pricing and firm entry. One lesson for developing countries considering bioprospecting agreements might be that economic problems might be avoided if economic and commerce agencies are involved in negotiations in earlier phases of negotiations.

## X. ASIAN YEW: OPEN ACCESS RESOURCES

In part because of the many problems taxol encountered in the United States, after 1993 Himalayan yew (*Taxus wallichiana*) and other Asian yew species became the main source of taxol. Harvesting was carried out in India, Nepal, and China under more or less open access conditions.<sup>171</sup> In Pakistan, taxol

168. See, e.g., *Bristol-Myers Squibb Co. v. IVAX Corp.*, 77 F. Supp. 2d 606, 609 (D.N.J. 2000); *Bristol-Myers Squibb Co. v. Ben Venue Labs.*, 90 F. Supp. 2d 522, 524 (D.N.J. 2000). Entry of generics was thus delayed until the end of 2000. By 2002, BMS's sales revenue for taxol was roughly halved from its 2000 high. U.S. GEN. ACCOUNTING OFFICE, *supra* note 56, at 16.

169. See, e.g., *Ohio et al. v. Bristol-Myers Squibb, Co.*, No.1:02-cv-01080 (EGS) (D.D.C. Nov. 19, 2003) (concerning the anti-cancer drug Taxol®).

170. Under the Hatch-Waxman Act, a brand-name company must submit information to the FDA on certain types of patents relating to its product. The FDA lists related patents to an approved drug in a publication known as the Orange Book. A firm seeking to market a generic version of a drug must certify to the FDA that the patents listed in the Orange Book either are invalid or will not be infringed by the generic drug. They must also notify the patent holder. If the patent holder files a patent infringement suit within 45 days of this notification, FDA approval to market the generic drug is automatically stayed for 30 months, without consideration of the merits of the suit. The FTC ruled that BMS abused the statutory 30-month stay of Hatch-Waxman by listing patents in the Orange Book that did not meet the listing criteria. BMS was able to make wrongful listings because the FDA does not review patents presented for listing in the Orange Book to determine whether they meet the statutory listing criteria. Once listed in the Orange Book, improperly-listed patents trigger a 30-month stay of generic approval. This delays generic entry and costs consumers millions dollars. See Press Release, U.S. Federal Trade Commission, *FTC Charges Bristol-Myers Squibb with Pattern of Abusing Government Processes to Stifle Generic Drug Competition* (March 7, 2003), available at <http://www.ftc.gov/opa/2003/03/bms.shtm>; see also U.S. Fed. Trade Comm'n, *In re Bristol-Myers Squibb Co.*, Agreement Containing Consent Order (FTC File Nos. 001-0221; 001-0046; 021-0181); U.S. Fed. Trade Comm'n, Analysis to Aid Public Comment In the Matter of Bristol-Myers Squibb Co. (FTC File Nos. 001-0221; 001-0046; 021-0181).

171. Cases of "[e]xcessive harvesting of *T. baccat* from the forests all along the Indian Himalaya for Taxol" are also reported in H.C.Rikhari, L.M.S. Palni, S. Sharma & S.K. Nandi, *Himalayan Yew: Stand Structure, Canopy Damage, Regeneration and Conservation Strategy*, 25 ENVTL. CONSERVATION 334 (1998).

production has been cited as contributing to the decline of the species, with estimated illegal extraction of leaves of 6,000 tons per year from 1996 to 2001.<sup>172</sup>

In 1995 Himalayan yew was listed in Appendix II of the Convention on International Trade in Endangered Species of Wild Fauna and Flora ("CITES").<sup>173</sup> CITES is an international agreement to regulate trade in threatened and endangered species. Appendix I species are those deemed threatened by extinction;<sup>174</sup> Appendix II species are not necessarily threatened with extinction but are subject to significant trade-related depletion. For Appendix II species, exporters must obtain permits from their home governments. Importers are required to inspect shipments for proper export permits, but import permits are not required. While Himalayan yew became a listed species, chemical extracts of yew (precursors to taxol) were exempt. Trade in chemical extracts, however, constituted the bulk of yew-related product trade.<sup>175</sup>

After 1995, trade in yew parts and derivatives from other Asian yews increased. China has become a major exporter of taxol. Large volumes of *Taxus yunnanensis* were exported from Myanmar to China and several United States pharmaceutical companies began importing *Taxus yunnanensis* from China. Today, *Taxus* species are scarce because of the illegal harvest for domestic extraction facilities.<sup>176</sup>

Medical demand for Chinese *Taxus* species has reduced their populations, especially in northwest Yunnan Province.<sup>177</sup> *Taxus* has been eliminated in Lidiping of Weixi County, Caojian of Yunlong County, and Rushui County.<sup>178</sup> *Taxus* species are listed as Endangered in the *China Plant Red Data Book: Rare and Endangered Plants*.<sup>179</sup> Schippmann estimated that 5,000-10,000 metric tons of bark and 2,000 metric tons of leaves have been harvested in Yunnan Province in recent years, while felling entire trees was part of harvesting practices.<sup>180</sup>

172. Convention on Int'l Trade in Endangered Species of Wild Fauna and Flora Secretariat, *Review of Significant Trade in Specimens of Appendix-II, Species Selection of Species for Trade Reviews after CoP13: Seven Asian Medicinal Species*. Fifteenth Meeting of the Plants Committee in Geneva, Switzerland (May 17-21, 2005). PC15, Doc. 10.2.2.

173. Convention on Int'l Trade in Endangered Species of Wild Fauna and Flora Secretariat, Appendices I, II and III, available at <http://www.cites.org/eng/app/appendices.shtml>.

174. *Id.*

175. Convention on Int'l Trade in Endangered Species of Wild Fauna and Flora Secretariat, *Proposal for Amendment of Appendices I and II, Proposition 48, Submitted by China and the United States*. Thirteenth Meeting of the Conference of Parties in Bangkok, Thailand (Oct. 2-14, 2004).

176. *Id.*

177. *Id.*

178. Convention on Int'l Trade in Endangered Species of Wild Fauna and Flora Secretariat, *Review of the Genus Taxus*. Eleventh Meeting of the Plants Committee in Langkawi, Malaysia (Sept. 3-7 2001). PC11, Doc. 22.

179. *Id.*

180. Uwe Schippmann, *Medicinal Plants Significant Trade Study*, CITES Project S-109. Doc. PC9 9.13 (rev.).

While the United States is the largest market for taxol, authorized and unauthorized production is significant in China. Harvest of taxol in China requires a permit, but illegally harvested materials are commonly seized. Good data is not available on how much Chinese-produced taxol is consumed domestically, exported to the United States, and exported illegally.<sup>181</sup>

At the thirteenth Conference of Parties to CITES in 2004, China and the United States jointly proposed that chemical extracts of *Taxus* species also be included in Appendix II and that the number of Asian yew species listed be expanded.<sup>182</sup> This proposal was accepted by other parties to the Convention. Today, however, Asian yews are listed by the World Wildlife Fund as among the ten species most threatened by illegal trade.<sup>183</sup>

## XI. THE FUTURE OF BIOPROSPECTING

Taxol is an interesting story, but are lessons from its development still relevant today? In the 1990s it appeared to some that bioprospecting and development of pharmaceuticals based on natural product might become obsolete.<sup>184</sup> Advances in high throughput screening and combinatorial chemistry meant that totally synthetic compounds could be produced and screened more cheaply than their natural counterparts. Synthesized molecules tended to be easier to scale up to commercial production and they also avoided the resource-supply difficulties of bioprospecting.<sup>185</sup> Further, securing patent protection was easier for chemically synthesized products. While some large pharmaceutical companies such as Bayer, Merck, and Wyeth maintained active natural products programs, others—GlaxoWellcome, SmithKlineFrench, and Pfizer—phased out their natural products screening programs.<sup>186</sup> Eli Lilly sold off its collection to a smaller research firm.<sup>187</sup>

Yet, the promise of combinatorial synthesis has remained largely unfulfilled. From January 1981 to June 2006, combinatorial chemistry was the source of discovery of only one approved drug.<sup>188</sup> Some scientists have noted that discovery of new active substances—known as New Chemical Entities—has

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181. Convention on Int'l Trade in Endangered Species of Wild Fauna and Flora Secretariat, *supra* note 176, at 5.

182. Convention on Int'l Trade in Endangered Species of Wild Fauna and Flora Secretariat, *supra* note 176, at 1–8.

183. World Wildlife Fund, *supra* note 55, at 8.

184. R.D. Firm, *Bioprospecting—Why Is It so Unrewarding?*, 12 BIODIVERSITY & CONSERVATION 207, 208 (2003).

185. *Id.*

186. J. Ortholand & A. Ganesan, *Natural Products and Combinatorial Chemistry: Back to the Future*, 8 CURRENT OPINION IN CHEMICAL BIOLOGY 271, 280 (2004).

187. A.M. Rouhi, *Betting on Natural Products for Cures*, 81 CHEMICAL ENGINEERING NEWS 93, 96–98, 100–03 (2003).

188. D. Newman & G.M. Cragg, *Natural Products as Sources of New Drugs over the Last 25 Years*, 70 J. NAT. PRODUCTS 461 (2007).

reached 25-year lows in recent years and that this drop in new drug discoveries has coincided with the shift away from natural products.<sup>189</sup>

Natural products remain a major source of drug discovery, either directly or as “blueprints” or “designs” for novel chemical structures. In a survey by NCI scientists, 63% of the 973 small-molecule New Chemical Entities approved as drugs worldwide from 1981 to June 2006 were based on natural products.<sup>190</sup> These included 6% that were natural products, 28% produced via semi-synthesis but derived from natural products, 5% produced via synthesis but whose molecular framework came from a natural product, and 24% were “natural product mimics” (i.e. synthetic compounds whose designs were based on natural products).<sup>191</sup> The relative contribution of natural products to drug discovery has even increased slightly since 2002.<sup>192</sup> The importance of drugs “based on” but not necessarily made from natural products suggests that genetic materials are serving more as sources of information rather than as raw materials in production.

There has been renewed interest in bioprospecting and natural products research with a number of smaller start-up firms now specializing in screening natural products collections. Rather than carry out in-house natural products programs, larger pharmaceutical companies may access promising leads via licensing agreements with these new start-ups.<sup>193</sup>

New areas of bioprospecting interest include the oceans and Antarctica.<sup>194</sup> It is not clear whether rules governing property rights over genetic resources in the Convention on Biological Diversity apply to the open sea or to Antarctica. Neither is it clear how rules governing resource use from the Law of the Sea or the Antarctic Treaty System affect bioprospecting. Given that these new regions of bioprospecting interest resemble open access regimes, it is perhaps a good thing that there is a trend toward using genetic materials as sources of information rather than directly, as production inputs.

## CONCLUSION

Advocates of bioprospecting have argued that forests can be managed as extractive reserves where genetic resources can be sustainably harvested for pharmaceutical development. Yet, the experience of taxol development in the United States illustrates how difficult this can be. The United States, a developed country with great scientific capacity, environmental protection mechanisms (such as the National Environmental Protection Act (NEPA)), centralized resource

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189. *Id.* at 461; A.M. Rouhi, *Rediscovering Natural Products*, 81 CHEMICAL ENGINEERING NEWS 77, 78, 82–33, 86, 88–91 (2003).

190. Newman & Cragg, *supra* note 188, at 467.

191. *Id.*

192. *Id.* at 472.

193. Ortholand & Ganesan, *supra* note 142, at 274; Rouhi, *supra* note 143.

194. See DAGMAR LOHAN & SAM JOHNSTON, BIOPROSPECTING IN ANTARCTICA. (2005), available at [http://www.ias.unu.edu/binaries2/antarctic\\_bioprospecting.pdf](http://www.ias.unu.edu/binaries2/antarctic_bioprospecting.pdf); B. Haefner, *Drugs from the Deep: Marine Natural Products as Drug Candidates*, DRUG DISCOVERY TODAY 8, 536–44 (2003); Gary Stix, *Patents on Ice: Antarctica as a Last Frontier for Bioprospectors—and their Intellectual Property*, SCI. AM., May 2004, at 48, 48.

management agencies (such as the Forest Service and BLM), and congressional oversight had difficulty developing harvesting plans. Indeed, harvesting guidelines for taxol required an act of Congress (the Pacific Yew Act). Even then, there were non-trivial cases of poaching and a shift of harvesting to private lands in the United States and foreign sources with less environmental regulation.

Taxol also illustrates that incentives for *in situ* resource conservation can be short-lived. From the start of the NCI-BMS CRADA in 1991, there were broad and concerted efforts to find alternative sources to the Pacific Northwest. These included plantation cultivation, tissue culture, and ultimately semi-synthesis. By 1994, the Pacific Northwest was no longer an important source of yew bark.

For countries considering bioprospecting contracts, a lesson is that there can be long time delays from program initiation to development of a marketable product. It took over 30 years from the time the Pacific yew bark was collected to the time the FDA approved taxol. The NCI-USDA screening program, which lasted 21 years, yielded taxol, an admitted blockbuster drug, but that has been the only product of that effort.

A curious aspect of taxol development was the fact that health agencies were put in charge of pricing and patent-length decisions. NCI, a medical research agency, negotiated the terms of the CRADA excluding the "reasonable price" clause. NCI's primary goal appeared to be to commercialize taxol quickly. Perhaps it could have driven a harder bargain with respect to the royalties it received or pricing conditions it placed on BMS. In bilateral negotiations, however, an "impatient" party is at a bargaining disadvantage.<sup>195</sup> It is uncertain how long the development of taxol would have been delayed had NCI held out for more favorable terms. Florida State University, however, appeared to extract a much better financial deal from BMS. The Hatch-Waxman Act, by allowing an automatic delay in the entry of generics and placing the FDA in charge of listing patents, again placed a health agency in charge of what is essentially anti-trust policy.

Another lesson is that the search and screening process was not the "one-off" variety specified in theoretical economic models. Compounds have a combination of attributes. Rather than rendering different species with the same chemical redundant, a discovery can increase the value of other species. The definition of a "hit" can also change over time (and this time frame can be quite long). It took a long time for a consensus to develop that taxol was a "hit" and assessments of its value changed several times with developments of new screening methods and approaches.

A final lesson we can draw from the experience of taxol is that simply creating a market demand for genetic resources with medical applications will not necessarily promote biodiversity conservation. Asian yews are being harvested rapidly in areas with less well-defined property-rights regimes, even where government policies designate them as "endangered." Bioprospecting can exchange one extinction threat (habitat conversion because a species is not valued)

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195. See, e.g., Ken Binmore, Ariel Rubinstein & Asher Wolinsky, *The Nash Bargaining Solution in Economic Modelling*, 17 RAND J. ECONOMICS 182-83 (1986).

for another (over-harvesting because the resource is valued in an open-access setting). To date, 64 plant species have been listed under CITES expressly because of the threat of over-harvest for medicinal uses.<sup>196</sup> The case of taxol illustrates that creating market demand for genetic resources without clearly defining property rights over them can lead to resource depletion rather than conservation. As the newest wave of bioprospecting focuses on the Antarctic, oceans, and other areas with more open-access property regimes, new questions will arise over bioprospecting's impact on biodiversity conservation.

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196. Schippmann, *supra* note 180.