BIOPROSPECTING AND THE CONVENTION ON BIOLOGICAL DIVERSITY

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Introduction

Of the estimated 250,000 known plant species in the world today, perhaps 5,000 have been screened for their medicinal potential. Yet, any one species could be the cure for a disease that is considered incurable. Consumers in the United States spend more than $6 billion annually on medicines derived from tropical plants. That lucrative market is the incentive pharmaceutical companies need to scour the rich rain forests of the tropics for the virtually limitless supply of active compounds, some of which could contain compounds for the next miracle drug.

- Conservation International[1]

Tremendous diversity characterizes life on earth.[2] Current best estimates range upwards of 100 million extant species.[3] Since the first unicellular organism arose more than one billion years ago, countless lineages of life have evolved along their own unique adaptive trajectories in response to environmental challenges and opportunities.[4] The result has been a bewildering variety of organisms that incorporate within themselves myriad biochemical and genetic solu-

[1] *See* `http://www.conservation.org/WEB/FIELDACT/C-C_PROG/ECON/biopros.htm`. This, and all websites listed below, visited March 25, 2000.

[2] *See* generally Edward O. Wilson, The Diversity of Life (1992).

[3] *See* Edward O. Wilson and Dan L. Perlman, Conserving Earth's Biodiversity CD-ROM (1999).

[4] *See id.*

tions to the challenges of survival and successful reproduction. Bioprospecting exploits these natural solutions to biological problems by attempting to harnass their potential for solving problems of interest and necessity to humans.

Bioprospecting is the exploration of biodiversity for commercially valuable genetic and biochemical resources.[5] Such resources can take many forms and have already been discovered within the extracts, cells, or genomes[6] of many organisms. They range from genes[7] to the biochemicals for which genes code[8] to the virtually limitless array of organic chemicals produced in chemical reactions, or cascades of multiple chemical reactions, mediated by polypeptides[9] or polynucleotides[10]. These derivatives of biodiversity have already played a large role in the development of many economically useful products.[11] A representative sample of the fruits of bioprospecting follow.

Probably the most oft-quoted bioprospecting success involves the rosy periwin-

[5] *See* Walter V. Reid et al., A New Lease on Life, in Biodiversity Prospecting: Using Genetic Resources for Sustainable Development (Eds. Walter V. Reid et al. Eds.) 1 (1993).

[6] A genome is All the genetic material in the chromosomes of a particular organism; its size is generally given as its total number of base pairs. *See* Life Science Dictionary, Biotech Resources and Indiana University `http://biotech.icmb.utexas.edu/search/dict-search.html` (2000).

[7] A gene is The fundamental physical and functional unit of heredity. A gene is an ordered sequence of nucleotides located in a particular position on a particular chromosome that encodes a specific functional product (i.e., a protein or RNA molecule). *See* Life Science Dictionary, Biotech Resources and Indiana University `http://biotech.icmb.utexas.edu/search/dict-search.html` (2000).

[8] Genes code for polypeptides and polynucleotides (either DNA or RNA). *See* Benjamin Lewin, Genes VII 29 (2000).

[9] A polypeptide (or protein) is A chain of peptides, or amino acids, usually less than 100 amino acids long. A polypeptide is formed during the process of translation. One or more polypeptides are required to make a protein. *See* Life Science Dictionary, Biotech Resources and Indiana University `http://biotech.icmb.utexas.edu/search/dict-search.html` (2000).

[10] A polynucleotide (i.e., DNA or RNA) is A covalently-linked sequence of nucleotides in which the 3' and 5' ends on each nucleotide are joined by phosphodiester bonds. *See* Life Science Dictionary, Biotech Resources and Indiana University `http://biotech.icmb.utexas.edu/search/dict-search.html` (2000)

[11] Derivatives of biodiversity have significantly contributed to the development drugs, botanical medicines, agricultural produce, ornamental horticulture, crop protection, cosmetics, and non-medical industrial processes.

kle (*Catharanthus roseus*) of the island of Madagascar. Biologist Edward O. Wilson provides a lyrical account in his book *The Diversity of Life*:

> An inconspicuous plant with a pink five-petaled flower, it produces two alkaloids, vinblastine and vincristine, that cure most victims of two the deadliest of concers, Hodgkin's disease, mostly afflicting young adults, and acute lymphoyctic leukemia, which used to be a virtual death sentence for children.[12]

Vinblastine and vincristine have also been found effective in treating Wilms' tumor, primary brain tumors, and testicular, cervical, and breast cancers.[13] Introduced in the 1960s by the Eli Lilly Company[14], these drugs derived from the rosy periwinkle have earned that company roughly $200 million in annual revenue.[15]

The neem tree (*Azirdirachta indica*), native to India and other parts of tropical Asia, and a near taxonomic relative of mahogany, has yielded a cornucopia of useful natural products. Neem extracts have been employed by Indian folk medicine against numerous ailments, including fevers and infections.[16] Indian researchers have isolated three substances from neem oil that are highly efficacious as contraceptives: DK-1 is a potent vaginal spermicide with the added benefit of being a powerful germicide; DNM-5 can be administered orally to prevent egg implantation early in pregnancy; and DNM-7 is an abortifacient.[17] By 1995, the United States Patent and Trademark Office had already granted more than 50 patents on chemicals derived from the neem tree.[18] Much controversy

[12] *See* Edward O. Wilson, The Diversity of Life 283 (1992).
[13] *See id.* 381.
[14] *See* `http://www.lilly.com/about/overview/milestones.html` (2000).
[15] *See* Edward O. Wilson, The Diversity of Life 283 (1992).
[16] *See* David Dickson and K.S. Jayaraman, *Aid groups back challenge to neem patents*, 377 Nature 95 (1995).
[17] *See* K.S. Jayaraman, *Neem unsheaths contraceptive potential*, 377 Nature 95 (1995).
[18] *See* David Dickson and K.S. Jayaraman, *Aid groups back challenge to neem patents*, 377

has surrounded an insecticide, whose active ingredient is azadirachtin, a chemical extracted from neem tree seeds. W.R. Grace & Company[19] received a U.S. patent on a method of extracting azadirachtin and stabilizing it in solution.[20] A coalition of international aid and environmental nongovernmental groups, including Jeremy Rifkin and the Foundation for Economic Trends, challenged the patent on grounds that traditional Indian folk use of neem extracts to control insects consituted prior art.[21] A similar challenge was mounted to invalidate a patent granted by the European Patent Office jointly to Grace and the U.S. Department of Agriculture for a neem-based fungicide.[22] Such was the value of this single species of tree that the market value of neem seeds reached $300 per tonne in 1995.[23]

The polymerase chain reaction (PCR) is one of the most important techniques in modern molecular biology and biochemistry and has been fundamental to the flowering of the entire biotechnology industry.[24] The PCR allows the identification and manipulation of extremely minute samples of DNA by amplifying as little as a single molecule of DNA into virtually unlimited quantities.[25] The technique was conceived by Kary Mullis, then a researcher at Cetus Corporation, who was subsequently awarded a Nobel Prize in Chemistry in 1993 for his dis-

Nature 95 (1995).

[19] *See* corporate homepage at `http://www.grace.com`.

[20] *See* David Dickson and K.S. Jayaraman, *Aid groups back challenge to neem patents*, 377 Nature 95 (1995).

[21] *See id.*

[22] *See id.*

[23] *See id.*

[24] Kary Mullis received the Nobel Prize in Chemistry in 1993 for his conception of the PCR barely a decade previous. *See* `http://nobelprizes.com/nobel/chemistry/1993a.html` (2000).

[25] *See* `http://nobelprizes.com/nobel/chemistry/1993a.html` (2000).

covery.[26] Mullis developed the PCR by employing a heat-tolerant enzyme called Taq polymerase, which is produced by a thermophilic[27] eubacterium (*Thermus acquaticus*) endemic to the hotsprings of Yellowstone National Park.[28] Cetus obtained a U.S. patent for the PCR process and then sold the rights to the process to Hoffman-LaRoche Ltd.[29] for more than $300 million.[30] Each year patents on the use of Taq polymerase in the PCR earn their owners more than $200 million.[31]

Hoping to replicate the success of Taq polymerase, biotechnology companies have begun searching for the next *Thermus acquaticus*. As *Science* reported in 1997:

> Prospectors are lining up to exploit the famous hot springs of Yellowstone National Park - not for minerals, but for the rugged microbes they contain, called thermophiles. U.S. National Park Service officials signed a pioneering contract that formally opened the hot springs to bioentrepreneurs on 17 August, as military bands, rangers on horseback, and Vice President Al Gore celebrated Yellowstone's 125^{th} anniversary.
>
> The initial agreement gives San Diego-based Diversa Corp. the right to commercialize thermophiles collected in the park in exchange for $175,000 over 5 years, plus a share of any profits. Park superintendent Michael Finley says deals like this will bring financial dividends and increase knowledge of the park's tiniest inhabitants. One good way to protect something, adds Diversa molecular biologist Eric Mathur, is to show it has value.[32]

It was such optimistic sentiments, along with the accelerating rate at which biodiversity was been destroyed by human activities[33], that inspired the United

[26] *See id.*

[27] Thermophilic refers to organisms that inhabit high temperatures habitats.

[28] *See generally* T.D. Brock and H. Freeze, *Thermus aquaticus gen. n., a nonsporulating extreme thermophile*, J. Bacteriol. 98:289-297 (1969). *See also* Michael Gross, Life on the Edge: Amazing Creatures Thriving in Extreme Environments 103-104 (1998).

[29] *See* corporate homepage at `http://www.roche.com` (2000).

[30] *See* J. St. George, *Status Report: Taq Patent Dispute*, 275 Science 1348 (1997).

[31] *See id.*

[32] *See* Eliot Marshall, *Yellowstone Opens the Gates to Biotech*, 227 Science 1027 (1997).

[33] *See* Edward O. Wilson and Dan L. Perlman, Conserving Earth's Biodiversity CD-ROM (1999).

Nations to sponser the Convention on Biological Diversity[34] (CBD) at the 1992 Rio Conference[35] and that motivated an overwhelming majority of the countries in the world to sign and ratify it[36].

If biodiversity represents a potentially valuable source of raw material for the biotechnology industry, its geographic distribution places the lion's share of this natural resource within the borders of poorer equatorial countries.[37] The CBD includes among its goals the conservation of biodiversity and the equitable sharing of the wealth generated therefrom between those countries rich in biotechnology and those rich in biodiversity.[38] Implementation of the CBD has led many source countries to attempt to restict legal access to their biodiversity in order to prevent commercial bioprospectors from freely exploiting those resources.[39] Such legal hurdles have added considerably to the transaction costs of bioprospecting. The sharing of profits from successful commercial products derived from biodiversity is often the *sine qua non* of such access agreements.[40]

[34] See U.N. Convention on Biological Diversity, June 2, 1992, U.N. Doc. DPI/130/7 (1992).

[35] Officially known as the 1992 United Nations Conference on Environment and Development.

[36] A total of 176 countries and the European Union (EU) have formally ratified the CBD. *See* `http://www.biodiv.org/conv/pdf/ratification-date.pdf` (2000). By comparison, the United Nations has 188 member states and two non-member states with permanent observer missions. *See* `http://www.un.org/Overview/missions.htm#nperm` (2000).

[37] *See* Edward O. Wilson and Dan L. Perlman, Conserving Earth's Biodiversity CD-ROM (1999).

[38] The text of CBD Article 1 states that The objectives of this Convention, to be pursued in accordance with the relevant provisions, are the conservation of biological diversity, the sustainable use of its components and the fair and equitable sharing of the benefits arising out of the utilization of genetic resources, including by appropriate access to genetic resources and by appropriate transfer of relevant technologies, taking into account all rights over those resources and to technologies, and by appropriate funding. *See* `http://www.biodiv.org/chm/conv/art1.htm` (2000).

[39] *See, e.g.*, Raúl O. Castillo, The Andean Common Code for the Access to Genetic Resources: A General Overview, in Global Genetic Resources: Access, Owneship, and Intellectual Property Rights (Eds. K. Elaine Hoagland and Amy Y. Rossman) (1997).

[40] *See, e.g.*, Eliot Marshall, *Yellowstone Opens the Gates to Biotech*, 227 Science 1027 (1997).

Furthermore, much debate has surrounded proposals to extend the ownership of intellectual property rights in inventions derived from biodiversity to the countries of geographic origin.[41] In short, the CBD has greatly altered the legal landscape in which commercial bioprospecting takes place.

This paper attempts to assess the economic value of biodiversity to commercial bioprospectors and source countries, surveys the provisions of the CBD that deal directly with bioprospecting, examines the types of legal access regimes being established by source countries, and considers the effects that new technologies like genomics and combinatorial chemistry will have on the future importance of bioprospecting.

Economics of Bioprospecting

Despite a wealth of anecdotal evidence, the economic value of bioprospecting has been difficult to estimate reliably. However, the issue has received renewed attention since the advent of the CBD due to the potential importance the resulting valuation might have as an incentive to conserve global biodiversity. A variety of methods have been employed to develop estimates of the economic use value[42] of biodiversity. Each has advantages and disadvantages. The range

[41] *See, e.g.*, Henry L. Shands and Amy Y. Rossland, Perspectives on Global Genetic Resources: Access, Ownership, and Intellectual Property Rights in Global Genetic Resources: Access, Owneship, and Intellectual Property Rights (Eds. K. Elaine Hoagland and Amy Y. Rossman) (1997).

[42] Use value here refers to the commercially useful natural products and genetic resources biodiversity can provide. Another use value not of direct relevance to this paper, but of potentially large magnitude, is the value of ecosystem services provided by biodiversity. *See generally* NATURE'S SERVICES (ED. GRETCHEN DAILY) (1997). Other values of bio-

of values estimated in different analyses spans multiple orders of magnitude. One approach is to estimate the economic value of bioprospecting from first principles. At the very least, this can provide reference value to evaluate estimates derived by other methods. Such an analysis is necessarily very rough and has large margins or error. What follow are the steps of calculation and the explicit assumptions of those calculations:

1.

Assume that the number of distinct species of extant organisms is roughly 10 million. Current best estimates range as high as 100 million species[43], so this is a conservative figure.

2.

Assume that the mean number of distinct genes in a species' genome is 10 000. Current best estimates suggest that the number of genes per genome ranges from a minimum of 500 for mycoplasma to a maximum of 100 000 for mammals.[44] Plants (50 000 genes)[45] and insects (12 000 genes)[46] comprise the vast majority of species[47], so an estimate of 10 000 genes per genome is also a conservative figure.[48]

diversity recognized by economics include its option value (that is, other uses that might be made of biodiversity in the future whose potential is preserved as long as biodiversity is not liquidated) and existence value (that is, the value people derive from knowing that biodiversity is still extant). *See generally* TOM TIETENBERG, ENVIRONMENTAL AND NATURAL RESOURCE ECONOMICS (5^{th}. Edition 2000).

[43] *See* Edward O. Wilson and Dan L. Perlman, Conserving Earth's Biodiversity CD-ROM (1999).

[44] *See* Benjamin Lewin, Genes VII 33 (2000).

[45] *See id.*

[46] *See id.*

[47] *See* Edward O. Wilson and Dan L. Perlman, Conserving Earth's Biodiversity CD-ROM (1999).

[48] Additional evidence suggests that this figure may significantly underestimate the mean genome size. When Celera Corporation determined the full genome sequence of the fruit fly (*Drosophila melanogaster*), initial analysis suggested that the fly's genome included almost 2 000 more genes than the 12 000 originally estimated. *See* Mark D. Adams et al., *The Genome Sequence of Drosophila melanogaster*, 287 Science 2185 (2000).

3.

Assume that only one gene out of every 100 000 genes could lead to a profitable[49] invention not duplicable by other genes. Given that the current rate at which genes have yielded profitable inventions is orders of magnitude greater than that assumed here[50], this figure is also conservative. This assumption likely holds even if one accounts for the costs of searching for profitable genes and developing their commercial potential.

4.

Therefore, the number of profitable genes represented by the earth's extant biodiversity is (10^7)x(10^4)x$(10^{-5}) = 1$ million profitable genes. Note that under less conservative assumptions the total number of non-redundant profitable genes would be much greater.

5.

If the annual average profitability of a profitable gene were $1 million, then the profits generated by profitable genes would generate $1 trillion per year. By comparison, if the annual average profitability were $10 million per profitable gene, then the total figure would rise to $10 trillion; with average profitability of $100 million, the total would rise to an extraordinary $100 trillion.

If any of the above assumptions are too conservative - a significant likelihood - then the profits available from genes could be even greater. It is notable that this rough calculation estimated only the profits from genes and completely discounted the value of natural products like those from the rosy periwinkle[51]

[49] Profitable here refers to a product having a present discounted value of greater than zero monetary units.

[50] Far fewer than 100 000 genes have ever been assayed, yet there are already many more than 10 profitable products derived from genes (e.g., alpha-interferon, erythropoietin).

[51] *See supra* note 11.

and the neem tree[52]. Given the deliberate use of conservative estimates in the calculation, it is reasonable to treat $1 trillion as a meaningful reference value. An estimate of such large magnitude indicates just how great might be the potential economic use value of biodiversity for bioprospecting.

A number of more sophisticated formal analyses have attempted to evaluate the economic worth of biodiversity for use in drug development. Some have concluded that the value of biodiversity is rather small[53] while others have suggested that its worth as a source for novel pharmaceuticals is potentially significant[54]. The latter have argued that the economic value of genes and natural products derived from biodiversity could provide a powerful incentive to conserve areas that are especially biodiverse.[55] It has also been suggested that bioprospecting could afford poorer countries a unique opportunity to develop their economies by spurring the development of domestic biotechnology industries.[56]

It is necessary to assess which of these claims is more accurate in order to determine whether bioprospecting is viable as a means for implementing the CBD.

[52] *See supra* note 15.

[53] *See generally* R. David. Simpson, Roger A. Sedjo, and John W. Reid, *Valuing Biodiversity for Use in Pharmaceutical Research*, 104 Journal of Political Economy (1996).

[54] *See generally* Gordon C. Rausser and Arthur A. Small, *Valuing Research Leads: Biodiversity and the Conservation of Genetic Resources*, 108 Journal of Political Economy (2000). *See also* R. Mendelsohn and M. Bailick, *The Value of Undiscovered Pharmaceuticals in Tropical Forests*, 49 Economic Botany (1995).

[55] *See generally* Norman R. Farnsworth, Djaja Doel Soejarto, *Potential Consequences of Plant Extinction in the United States on the Availability of Prescription Drugs*, 39 Economic Botany 231-240 (1985). *See also generally* Peter Principe, The Economic Value of Biodiversity among Medicinal Plants (1989). *See also* Edward O. Wilson, The Diversity of Life 281-310 (1992). *See also generally* Walter V. Reid et al., A New Lease on Life in Biodiversity Prospecting: Using Genetic Resources for Sustainable Development (EDs. Walter V. Reid et al.) (1993). *See also generally* Steven M. Rubin and Stanwood C. Fish, *Biodiversity Prospecting: Using Innovative Contractual Provisions to Foster Ethnobotanical Knowledge, Technology, and Conservation*, 5 Colorado Journal of International Law and Policy 23-58 (1994).

[56] *See generally* Charles Weiss and Thomas Eisner, *Partnerships for value-added through bioprospecting*, 20 Technology In Society (1998).

If it is determined that biodiversity possesses a high economic use value, then the potential may exist for resulting economic benefits that could, in theory, be equitably shared.[57] On the other hand, if pessimistic estimates are more accurate, and biodiversity holds little economic use value, then there may be few benefits available for sharing, equitable or otherwise.

Economist R. David Simpson, currently of the World Resources Institute[58], has developed an innovative analytic framework for calculating the economic value of biodiversity in terms of its potential for the development of pharmaceutical products.[59] The model upon which his analyses are based attempts to take into account the way in which novel pharmaceuticals are discovered:

> Pharmaceutical research on natural products is more often intended to develop leads than to identify natural products that can be used in an essentially unmodified form. Leads are promising molecules: blueprints of compounds that must be modified to increase efficacy or reduce side effects. Part of the reason for the increased recent interest in natural products research is a renewed appreciation of the importance of natural leads. While considerable efforts at rational design of drugs from inorganic materials continue, researchers have also come to recognize that nature has perfected chemicals that synthetic chemists might never dream up.[60]

Genetic resources and natural products are assumed to be nonrival goods[61], meaning that use of any particular lead by one will not prevent the equivalent use by others. The model takes into account the evolving national and international legal frameworks in which the aspirations of the CBD are being implemented either *de facto* (in the form of contracts between commerical bioprospectors

[57] *See, e.g.*, CBD Article 1 `http://www.biodiv.org/chm/conv/art1.htm` (2000).
[58] *See* organization hompage `http://www.wri.org` (2000).
[59] *See, e.g.*, R. David. Simpson, Roger A. Sedjo, and John W. Reid, *Valuing Biodiversity for Use in Pharmaceutical Research*, 104 Journal of Political Economy (1996).
[60] *See* R. David. Simpson, Roger A. Sedjo, and John W. Reid, *Valuing Biodiversity for Use in Pharmaceutical Research*, 104 Journal of Political Economy 166 (1996).
[61] *See id.*

and biodiversity source countries) or *de jure* (in the form of formally legislated access agreements that govern availability to and use of biodiversity resources).[62] The analysis also relies on the assumption that the full set of genetic resources contained within all of biodiversity contains significant redundancy with respect to the provision of pharmaceutical leads.[63] The model and its predictions are described as follows:

> [We] derive a simple demand function for biodiversity in pharmaceutical research, determine the willingness to pay for the marginal species, and consider the sensitivity of the value of the marginal species to the probability of discovery and assumptions concerning overall profitability. The intuition behind our results is easily grasped by considering extreme cases. If all species are promising sources of leads, most would be redundant and the marginal species close to valueless. If no species are likely sources of leads, it is unlikely that two or more will prove redundant but also unlikely that *any* species will prove to have value. Increasing the likelihood of success with any species has two offsetting effects on the value of the marginal species: it increases the expected payoff in the event the species is tested, but it also decreases the expected payoff inasmuch as it is more likely that another equally valuable species is discovered first. By identifying the probability of success at which these effects are balanced, we can derive an upper bound on the value of the marginal species. As the number of species available for testing increases, this upper bound declines.[64]

Using a number of optimistic assumptions and empirical data regarding the sources and development costs of new drugs, the analysis yielded an estimate

[62] *See id.* 166-167.

[63] *See* R. David. Simpson, Roger A. Sedjo, and John W. Reid, *Valuing Biodiversity for Use in Pharmaceutical Research*, 104 Journal of Political Economy 168-169 (1996) ([There] are several reasons why genetic resources may be relatively redundant. First, the same species may be found over a wide range. If all representatives of a species produce a particular compound, individuals in excess of the number needed to maintain a viable population are redundant. Second, there are numerous instances in which indentical drugs, or drugs with similar clinical properties, have been isolated from different species...It may also be the case that there are a host of other sources of common compounds that remain undiscovered because current sources are adequate. Given the numerous examples of parallel morphological development in the evolution literature, it should not be surprising to find that different organisms that have evolved in similar ecological niches have developed similar chemicals.Finally, there is a dimension of what we might call medicinal redundancy. Different therapeutic mechanisms may be effective in treating the same symptoms. Moreover, while the inventiveness of nature in developing useful compounds is much extolled as a factor in the increased demand for natural products for pharmacological research, synthesis from nonorganic sources may also yield substitutes for natural product leads.).

[64] *See id.* 169.

that the maximum value of the marginal species was $9 431; this translates into a maximum economic value for bioprospecting of $20 per hectare in the most biodiverse region on earth - western Ecuador - and considerably less elsewhere.[65] The authors conclude:

> [Given reasonable assumptions] it seems quite likely that the perceived value of the marginal species will be miniscule. This view seems to be consistent with information concerning observed transactions. This subject should be studied further, but we would not expect a reversal of the conclusion of our analysis: the private value of the marginal species for use in pharmaceutical research and, by extension, the incentive to conserve the marginal hectare of threatened habitat are negligible.[66]

Thus, under this model, bioprospecting would appear to be an economically questionable endeavor, and would be unlikely to provide sufficient incentives to conserve biodiversity through the equitable sharing of benefits envisioned by the framers of the CBD.[67]

A subsequent analysis adapted the model of Simpson et al. to reflect more accurately the great importance of information rents in drug development.[68] It criticized the accuracy of results generated using the original model.[69] The

[65] *See id.* 180.

[66] *See id.* 183.

[67] *See, e.g.*, CBD Article 1 `http://www.biodiv.org/chm/conv/art1.htm` (2000).

[68] *See generally* Gordon C. Rausser and Arthur A. Small, *Valuing Research Leads: Bioprospecting and the Conservation of Genetic Resources*, 108 Journal of Political Economy (2000).

[69] *See id.* 174-175. ([The conclusion reached using the previous model] flows specifically from a stylized description of the research process as one of brute-force testing, unaided by an organizing scientific framework. Given the progress of biological and ecological science, the realism of this assumption is suspect. While exceptions can be noted, it is a powerfully general rule that no one ever searches for anything by examining large collections of objects in random order. The essence of efficient search is the identification of clues that allow the universe of potential leads to be narrowed down. Expensive tests are then conducted, ideally, only on that handful of prospects that show special promise. In research targeting the development of innovations, the clues that identify those prospects are provided by scientific models - maps of the world that highlight areas in which the productivity of research effort is likely to be highest. The ability of models to point out rich veins of ore explains exactly why applied researchers acquaint themselves with basic theory. It is substantially from this ability that the human capital of an applied research scientist derives its value. Brute-force search - the

amended analysis was structured to account explicitly for the importance of information rents for promising leads:

> [In bioprospecting], leads of unusual promise are distinguished with the aid of scientific information gleaned from fields such as ecology and taxonomy. Researchers can, and do, draw on rich bases of publicly available data describing the location and properties of plants, animals, and microbes, their evolutionary history, and their survival and reproductive strategies. These data, when filtered through a model that makes sense of them, can serve to tag those creatures most likely to display economically valuable characteristics. Just as a catalog helps a library patron to focus quickly on those few volumes that are most likely to contain information she desires, so can an ecological model parse the living world into categories suggesting potential use.
>
> Through product differentiation, scientific understanding generates information rents: if a particular lead is believed to show promise as an aid to a lucrative research discovery, a rational investigator will be willing to pay an access fee. This principle is fundamental to understanding how genetic resources will be, or should be, valued in the marketplace. In particular, it is central to an analysis that identifies conditions under which bioprospecting creates effective market-based financial incentives for biodiversity conservation. Rents accrue to the owners of leads as they absorb part of the knowledge spillovers generated by publicly available science.[70]

Using the same numerical examples employed by Simpson et al.[71], results from the amended model showed biodiversity as possessing much greater economic value for bioprospecting.[72] For example, the amended model valued a hectare of western Ecuador at almost $9 200 for purposes of bioprospecting, or roughly 450 times greater than that calculated by Simpson et al.[73] Such a result suggests that significant economic benefits might attend bioprospecting.

Another method used to assess the economic value of biodiversity for bio-

sequential testing of large numbers of leads in no particular order - is by contrast a nearly cost-maximizing approach to discovery. It is deployed, if at all, only as a backstop technology, when all possibilities for directed search have been exhausted.).

[70] *See id.* 176.

[71] *See* R. David. Simpson, Roger A. Sedjo, and John W. Reid, *Valuing Biodiversity for Use in Pharmaceutical Research*, 104 Journal of Political Economy 178 (Table 2) (1996).

[72] *See* Gordon C. Rausser and Arthur A. Small, *Valuing Research Leads: Bioprospecting and the Conservation of Genetic Resources*, 108 Journal of Political Economy 194 (2000).

[73] *See id.* 193-194 (especially Table 1).

prospecting involves analyzing the sources of drugs already on the market. The most comprehesive such assessment conducted to date concluded that most of the top 150 brand name drugs prescribed in the U.S. in 1993[74] contain a compound derived from or patterned after a constituent of biodiversity.[75] The study concluded that 57% of the top 150 prescription drugs were derived directly or indirectly from biodiversity: 23% from animals, 18% from plants, 11% from fungi, 4% from bacteria[76], and 1% from marine organisms.[77] Some individual species were found to provide the source for multiple drugs in the top 150, the most prodigious being opium poppy (*Papaver somniferum*) with 15, joint fir (*Ephedra sinica*) with 11, bread mold (*Penicillium notatum*) with 9, a fungus (*Cephalosporium acremonium*) with 7, Brazilian fer-de-lance (*Bothrops jararaca*) and a eubacterium (*Streptomyces erythreus*) with 4 each, and human (*Homo sapiens*) with 3.[78] Given the huge research and development costs of successfully bringing a new drug to market - estimated to average $300-500 million[79] - these results suggest biodiversity as an important, possibly even the most important, avenue for the discovery and development of new drugs.

Direct estimates have been also been attempted on the magnitude of the annual

[74] From January to September.

[75] *See generally* Francesca Grifo, David Newman, Alexandra S. Fairfield, Bhaswati Bhattacharya, and John T. Grupenhoff, The Origins of Prescription Drugs in Biodiversity and Human Health (Eds. Francesca Grifo and Joshua Rosenthal) (1997).

[76] Although the authors do not specify what is meant by this term, it is likely that organisms grouped under this heading are mostly eubacteria rather than archaea. Formerly, both eubacteria and arachaea were grouped under the arbitrary label bacteria, but are now recognized to be widely divergent lineages of life. *See* `http://phylogeny.arizona.edu/tree/life.html` (2000). *See also* D.M. Ward, *A natural species concept for prokaryotes*, 1 Current Opinion In Microbiology 271-277 (1998).

[77] *See* Francesca Grifo, David Newman, Alexandra S. Fairfield, Bhaswati Bhattacharya, and John T. Grupenhoff, The Origins of Prescription Drugs in Biodiversity and Human Health (Eds. Francesca Grifo and Joshua Rosenthal) 137 (Table 6.2) (1997).

[78] *See id.* 138.

[79] *See* Bruce Agnew, *When Pharma Merges, R & D Is the Dowry*, 287 Science 1952 (2000).

markets for commercial products derived from biodiversity (including both natural products and genetic resources).[80] Because the margins of error in these calculations are considerable, both high and low estimates were developed (Table 1).

Table 1. Estimates for Annual Markets for Products Derived from Biodiversity[81]

Sector	Market (US$ billion) LOW	Market (US$ billion) HIGH
Pharmaceuticals	75	150
Botanical medicines	20	40
Agricultural produce	300+	450+
Ornamental plants	16	19
Crop protection products	0.6	3
Other biotechnology	60	120
Personal care & cosmetics	2.8	2.8
Rounded total	500	800

These estimates also suggest that products derived directly or indirectly from biodiversity possess significant economic value. In fact, when pharmaceuticals (the subjects of the analyses presented above) are considered along with other commercial products derived from biodiversity, the total economic value of biodiversity is considerable. Interestingly, the high estimate of the total in Table 1 ($800 billion) is quite similar to the estimate derived from first principles at

[80] *See* Kerry ten Kate and Sarah A. Laird, The Commercial Use of Biodiversity - Access to Genetic Resources and Benefit-Sharing 57 (1999).

[81] This table is fully adapted from Kerry ten Kate and Sarah A. Laird, The Commercial Use of Biodiversity - Access to Genetic Resources and Benefit-Sharing 2 (Table 1.1) (1999).

the beginning of this section ($1 trillion).

In short, the weight of evidence from the few formal studies to assess the economic use value of biodiversity suggests that its worth may be considerable. Consequently, bioprospecting may indeed have the potential to generate significant economic benefits, a necessary condition for the fair and equitable sharing of those benefits envisioned by the CBD.[82]

The Convention on Biological Diversity

The Convention on Biological Diversity's objectives are the conservation of biological diversity, the sustainable use of its components and the fair and equitable sharing of the benefits arising out of the utilization of genetic resources. The Convention is thus the first global, comprehensive agreement to address all aspects of biological diversity: genetic resources, species, and ecosystems. It recognizes - for the first time - that the conservation of biological diversity is a common concern of humankind and an integral part of the development process. To achieve its objectives, the Convention - in accordance with the spirit of the Rio Declaration on Environment and Development - promotes a renewed partnership among countries. Its provisions on scientific and technical cooperation, access to genetic resources, and the transfer of environmentally sound technologies form the foundations of this partnership.

- United Nations Biodiversity Secretariat[83]

The Convention on Biological Diversity is a distinctive source of international law. It serves two main purposes.[84] First, it is an international treaty whose explicit goal is to conserve biodiversity comprehensively and at the global level. Its scope is unprecedented in comparison to any other laws regarding the

[82] *See, e.g.*, CBD Article 1 http://www.biodiv.org/chm/conv/art1.htm (2000).
[83] *See* `http://www.biodiv.org` (2000).
[84] *See* `http://www.biodiv.org/chm/conv/art1.htm` (2000).

conservation of biodiversity. Second, it provides an institutional framework for the promotion of scientific study of biodiversity, the development of policy for its conservation and sustainable and equitable use, and the implementation of legal mechanisms substantively to realize policy goals.

Other legal efforts to conserve biodiversity have been much more limited in scope than the CBD. National laws, such as the U.S. Endangered Species Act[85], have attempted to conserve specific levels of biodiversity within the geographic boundaries of individual countries. International treaties, such as the Convention on International Trade in Endangered Species of Wild Flora and Fauna (CITES)[86] and the International Convention for the Regulation of Whaling (ICRW)[87], have restricted themselves to well defined subsets of biodiversity. In stark contrast, the CBD states as its first and unqualified objective the conservation of biological diversity.[88]

Over the course of the 1980s, pressure mounted for a more comprehensive approach to the conservation of biodiversity.[89] In 1982, the U.N. General Assembly passed the World Charter on Nature, a merely hortatory and nonbinding statement about the value of conserving nature. Then, in 1987, the United Nations Environment Program (UNEP) set up a working group to investigate the pos-

[85] *See* 16 U.S.C. §§ 1531 et seq.

[86] *See* Convention on International Trade in Endangered Species of Wild Fauna and Flora, March 3, 1973 `http://www.cites.org/CITES/eng/index.shtml` (2000). (An international agreement that regulates and restricts trade in rare species or parts thereof.).

[87] *See* International Convention for the Regulation of Whaling, Dec. 2, 1946 `http://ourworld.compuserve.com/homepages/iwcoffice/IWC.htm` (2000). (An international agreement, administered through the International Whaling Commission, originally established to manage the harvesting of whales at sustainable levels but that currently imposes a moratorium on commerical whaling.).

[88] *See* `http://www.biodiv.org/chm/conv/art1.htm` (2000).

[89] The history of the negotiation and implementation of the CBD that follows is based on personal communications from Wendy E. Franz, international environmental politics scholar in the Department of Government, Harvard University (2000).

sibility of an international treaty to conserve biodiversity in a comprehensive manner. In 1991, this working group became the Intergovernmental Negotiating Committee for a Convention on Biological Diversity.

The result was the Convention on Biological Diversity, which was opened to participating countries for signature in 1992 at the United Nations Conference on the Environment and Development (UNCED) in Rio. Article 1 of the CBD summarizes its content and scope:

> Article 1. Objectives.
> The objectives of this Convention, to be pursued in accordance with its relevant provisions, are the conservation of biological diversity, the sustainable use of its components and the fair and equitable sharing of the benefits arising out of the utilization of genetic resources, including by appropriate access to genetic resources and by appropriate transfer of relevant technologies, taking into account all rights over those resources and to technologies, and by appropriate funding.[90]

A total of 176 countries and the European Union (EU) have formally ratified the CBD.[91]

Although the original purpose envisioned for the treaty was simply the comprehensive international conservation of biodiversity, many developing countries balked at such a single-minded objective, judging it an expensive unfunded mandate they could ill afford. Furthermore, they demanded a fair share of whatever economic benefits flowed from the biodiversity they would be expected to conserve. In response to the threat of boycott by the very countries that housed most of the earth's biodiversity, the final draft of the CBD emphasized access to genetic resources and fair and equitable sharing of the benefits flowing from

[90] *See* `http://www.biodiv.org/chm/conv/art1.htm` (2000).
[91] *See* `http://www.biodiv.org/conv/pdf/ratification-date.pdf` (2000).

these resources. Consequently, the text of the CBD contains numerous provisions that deal specifically with the economic benefits of biodiversity. They are considered in order below.

This first provision of the CBD that deals specifically with bioprospecting activities is Article 8[92](j). It provides that

> [Each Contracting Party shall, as far as possible and as appropriate:] Subject to its national legislation, respect, preserve and maintain knowledge, innovations and practices of indigenous and local communities embodying traditional lifestyles relevant for the conservation and sustainable use of biological diversity and promote their wider application with the approval and involvement of the holders of such knowledge, innovations and practices and encourage the equitable sharing of the benefits arising from the utilization of such knowledge, innovations and practices[93]

This provision appears to effect the practice of bioprospecting in two main ways. First, it emphasizes the value and encourages the efficient use of traditional knowledge gathered by indigenous and local peoples to develop useful or marketable biodiversity-based products. However, it also places practical limitations on such uses and insists that they should be voluntary and that the benefits therefrom should be shared with those whose knowledge contributed to a product. An implicit requirement of this provision may be the securing of prior informed consent from the relevant indigenous or local people for the bioprospecting activity contemplated.[94]

Article 15[95] deals most directly and comprehensively with the use and legal treatment of genetic resources. Its seven provisions are reproduced below:

[92] CBD Article 8 is entitled In-situ Conservation.
[93] *See* `http://www.biodiv.org/chm/conv/art8.htm` (2000).
[94] *See* Kerry ten Kate and Sarah A. Laird, The Commercial Use of Biodiversity - Access to Genetic Resources and Benefit-Sharing 20 (1999).
[95] CBD Article 15 is entitled Access to Genetic Resources.

1 Recognizing the sovereign rights of States over their natural resources, the authority to determine access to genetic resources rests with the national governments and is subject to national legislation.
2 Each Contracting Party shall endeavour to create conditions to facilitate access to genetic resources for environmentally sound uses by other Contracting Parties and not to impose restrictions that run counter to the objectives of this Convention.
3 For the purpose of this Convention, the genetic resources being provided by a Contracting Party, as referred to in this Article and Articles 16 and 19, are only those that are provided by Contracting Parties that are countries of origin of such resources or by the Parties that have acquired the genetic resources in accordance with this Convention.
4 Access, where granted, shall be on mutually agreed terms and subject to the provisions of this Article.
5 Access to genetic resources shall be subject to prior informed consent of the Contracting Party providing such resources, unless otherwise determined by that Party.
6 Each Contracting Party shall endeavour to develop and carry out scientific research based on genetic resources provided by other Contracting Parties with the full participation of, and where possible in, such Contracting Parties.
7 Each Contracting Party shall take legislative, administrative or policy measures, as appropriate, and in accordance with Articles 16 and 19 and, where necessary, through the financial mechanism established by Articles 20 and 21 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.[96]

Article 15 is important to the practice of bioprospecting for a variety of reasons, but foremost for its explicit recognition in international law that states possess sovereign rights over their natural resources (including biodiversity) and can use these sovereign rights to establish legal regimes governing access to those resources. Previous to this formal recognition there existed much uncertainty and dispute regarding ownership over biodiversity. Many considered - and still consider - biodiversity to be the collectively owned inheritance of all mankind or

[96] *See* `http://www.biodiv.org/chm/conv/art15.htm` (2000).

the unowned commons of nature[97] However, more control over the biodiversity within their own borders was a key demand by many developing countries and their *sine qua non* for agreeing to the CBD.[98]

Acting as a counterweight to Article 15.1, Article 15.2 creates an obligation for states to facilitate access to their genetic resources. Article 15.3 further lessens burdens on access by appearing to exempt biodiversity resources collected before the CBD entered into legal force[99]. Since the long history of bioprospecting resulted in the collection of many biological samples (and their deposit elsewhere than in the source country) before the CBD, Article 15.3 may create a significant legal avenue for use of biodiversity unauthorized by the country of origin. This could offer potential benefits to institutions such as museums, herbaria, and botanical gardens whose collections include vast quantities of potentially valuable biodiversity.[100] It could also present a competitive threat to source countries for potential bioprospecting revenue by offering commercial bioprospectors an alternative source of biodiversity. Article 15.3 similarly exempts biodiversity collected in countries outside the CBD; however, given the high success rate of CBD ratification[101], this loophole is of minor importance.

[97] *See Guidelines for the Ecological Sustainability of Nonconsumptive and Consumptive Uses of Wild Species*, Article 10(b), Annex 1, IUCN Gen. Ass. Paper, G.A./19/94/3 (1994). For additional information about the International Union for the Conservation of Nature (IUCN) see organization homepage at `http://iucn.org/index.html` (2000).

[98] Personal communications from Wendy E. Franz, international environmental politics scholar in the Department of Government, Harvard University (2000).

[99] The CBD became legally binding on its signatories on December 29, 1993, 90 days after the 30th ratification. *See* `http://www.biodiv.org/conv/BACKGROUND.HTML` (2000).

[100] *See, e.g.*, Alan Dove, *Botanical Gardens Cope With Bioprospecting Loophole*, 281 Science 1273 (1998).

[101] A total of 176 countries and the European Union (EU) have formally ratified the CBD. *See* `http://www.biodiv.org/conv/pdf/ratification-date.pdf` (2000). By comparison, the United Nations has 188 member states and two non-member states with permanent observer missions. *See* `http://www.un.org/Overview/missions.htm#nperm` (2000).

Articles 15.4 and 15.5 provide a framework for proper behavior between source states and prospective bioprospectors interested in gaining access to genetic resources. There are two general conditions.

The first part of Article 15.4 - Access, where granted - suggests that source states do not have to agree to provide access at all. However, if access is to be granted, it shall be on mutually agreed terms between the source state and the party seeking access. This grants the source state a great advantage during negotiation because it can hold out for any terms it desires to be incorporated in an access agreement, providing that such terms are consistent with the whole of the CBD. The types of terms intended by this provision probably include those that specify how the genetic resources of interest are to be legally acquired (e.g., precisely where collecting may be conducted, what manner of collection is permitted, under what sort of supervision collecting is to occur), what uses of collected material are permitted (e.g., where research may be conducted, whether material may be sold to others), how access to the material may be restricted in the future, and how the source country and bioprospector intend to share benefits arising from research on, and development of, any biodiversity collected.[102]

In addition to the detailed requirements of Article 15.4, Article 15.5 stipulates that Access to genetic resources shall be subject to prior informed consent of the Contracting Party providing such resources. This also strengthens the hand of source countries because it requires full disclosure by bioprospector of informa-

[102] *See* Kerry ten Kate and Sarah A. Laird, The Commercial Use of Biodiversity - Access to Genetic Resources and Benefit-Sharing 22 (1999).

tion pertinent to the negotiation of an access agreement. Prior informed consent implies several necessary conditions to an access agreement.[103] Informed consent must be granted before the activity contemplated in the access agreement may commence. Consent must be made in the context of full and truthful disclosure by the bioprospector regarding how, where, and from what source he intends to collect the relevant genetic resources, what specific uses, commercial or otherwise, he contemplates for those resources, and whether any third party not involved in negotiating the access agreement will gain access to the resources themselves or to any benefits flowing from them. Consent certainly refers to the source country, but whether it also applies to other interested parties, such as local or indigenous groups, is ambiguous. Prudent bioprospectors would likely benefit from securing prior informed consent from as many interested parties as feasible to avoid potentially costly complications. Finally, the text of Article 15.5 appears allow a source country to exempt bioprospectors from having to obtain prior informed consent. It is possible that bioprospectors who contemplate becoming repeat players in a particular source country could earn themselves future preferential treatment by ensuring that they act with obvious good faith in scrupulously observing all the terms of their access agreement during the course of their activities.

Article 15.6 is a hortatory provision that promotes two goals. First, states are urged to promote scientific research into the beneficial uses of genetic resources. Increased levels of scientific research may have the salutary effect of increasing

[103] *See id.* 27.

the real and perceived economic valuation of *in situ* biodiversity, thus accelerating the accrual of benefits to both bioprospectors and source countries. Second, any such research is to be conducted with the full participation of the source country, and, ideally, within the borders of the source state. The sort of benefits that might result from such cooperative research initiatives include scientific and technical training of source country personnel and enhanced alignment of interests in conserving biodiversity between source country, bioprospectors, and any other parties to whom resulting benefits flow. The importance of this provision is probably minor due to its merely hortatory nature and the likelihood that negotiations aimed at reaching access agreements undertaken in the context of Article 15.4 will already have considered the inclusion or exclusion of such terms into potential agreements.

Article 15.7 is also merely hortatory in nature. It urges countries that benefit from the fruits of bioprospecting (e.g., new biotechnologies, medicines, or agricultural products) to share those benefits equitably with countries from whose biodiversity such benefits were developed. However, they are granted a large degree of discretion, and can employ whichever means they deem appropriate. Even so, such agreements must still provide for mutually agreed terms.

Article 15.7 would seem to be directed more forcefully to benefits developed by the government of the source country itself, rather than non-governmental actors. The National Cancer Institute[104] (NCI), a member of the U.S. National Institutes of Health[105], provides a useful example of how this provision might

[104] *See* agency homepage at `http://www.nci.nih.gov` (2000).
[105] *See* agency homepage at `http://www.nih.gov/icd` (2000).

be implemented. The NCI operates a large program to screen natural products collected around the world for efficacy against cancer.[106] The NCI requires companies that commercialize products deemed promising in this screening process to take part in a three-way contractual relationship called triangular privity: this arrangement involves separate legally binding agreements between NCI and the source country, NCI and its licensee, and source country and NCI licensee.[107] The successful achievement of triangular privity necessarily involves more time and higher transaction costs than the negotiation of a typical two-party contract. However, it has two distinct advantages: (1) it demonstrates compliance with the CBD by a part of the U.S. government; (2) it fosters good relations with biodiversity source countries, helping to assure the continued access to bioprospecting upon which NCI depends for leads in the search for new cancer treatments.

Article 16.3[108] urges that any technology developed using a source country's genetic resources be transfered back to that source country on favorable terms. Specifically, it provides:

> Each Contracting Party shall take legislative, administrative or policy measures, as appropriate, with the aim that Contracting Parties, in particular those that are developing countries, which provide genetic resources are provided access to and transfer of technology which makes use of those resources, on mutually agreed terms, including technology protected by patents and other intellectual property rights, where necessary, through the provisions of Articles 20 and

[106] See Thomas D. Mays, Kate Duffy-Mazan, Gordon Cragg, and Michael Boyd, A Paradigm for the Equitable Sharing of Benefits Resulting from Biodiversity Research and Development in Biodiversity and Human Health (Eds. Francesca Grifo and Joshua Rosenthal) 267-270 (1997).

[107] *See generally* T.D. Mays, K. Duffy-Mazan, G. Cragg, and M. Boyd, Triangular Privity - A Working Paradigm for the Equitable Sharing of Benefits from Biodiversity Research and Development in Global Genetic Resources: Access, Owneship, and Intellectual Property Rights (Eds. K. Elaine Hoagland and Amy Y. Rossman) (1997).

[108] CBD Article 16 is entitled Access to and Transfer of Technology.

21 and in accordance with international law and consistent with paragraphs 4 and 5 below.[109]

Implementation of this provision is substantially complicated by three modifying phrases: as appropriate, on mutually agreed terms, and where necessary. It is further complicated by its potential conflict with both national and TRIPs legal regimes for patent protection.[110] However, its attempt to align the incentives for the conservation of biodiversity of both source countries and other countries deriving benefits from bioprospecting accords well with the first main goal of the CBD[111].

Article 19.1 and 19.2 echo and reinforce Articles 15.6, 15.7, and 16.3 by attempting to ensure that source countries participate in and receive benefits from the research and development made possible by bioprospecting for their genetic resources. Article 19.1 and 19.2 provide specifically:

1 Each Contracting Party shall take legislative, administrative or policy measures, as appropriate, to provide for the effective participation in biotechnological research activities by those Contracting Parties, especially developing countries, which provide the genetic resources for such research, and where feasible in such Contracting Parties.
2 Each Contracting Party shall take all practicable measures to promote and advance priority access on a fair and equitable basis by Contracting Parties, especially developing countries, to the results and benefits arising from biotechnologies based upon genetic resources provided by those Contracting Parties. Such access shall be on mutually agreed terms.[112]

[109] *See* `http://www.biodiv.org/chm/conv/art16.htm` (2000).
[110] It is premature to decide how the intellectual property provisions in Article 16.3 of the CBD will interact with the WTO-TRIPs agreement negotiated subsequently. *See* organization homepage at `http://www.wto.org` (2000). Such interaction may be significant because membership in these two agreements overlaps substantially.
[111] The first objective listed in the text of the CBD Article 1 is the conservation of biological diversity. *See* `http://www.biodiv.org/chm/conv/art1.htm` (2000).
[112] *See* `http://www.biodiv.org/chm/conv/art19.htm` (2000).

However, Article 19 also serves a second distinct function that is likely to have an increasing, though indirect, impact on bioprospecting for genetic resources. It provides guidelines for what has become known as biosafety[113]. The text specifically provides:

> 3 The Parties shall consider the need for and modalities of a protocol setting out appropriate procedures, including, in particular, advance informed agreement, in the field of the safe transfer, handling and use of any living modified organism resulting from biotechnology that may have adverse effect on the conservation and sustainable use of biological diversity.
> 4 Each Contracting Party shall, directly or by requiring any natural or legal person under its jurisdiction providing the organisms referred to in paragraph 3 above, provide any available information about the use and safety regulations required by that Contracting Party in handling such organisms, as well as any available information on the potential adverse impact of the specific organisms concerned to the Contracting Party into which those organisms are to be introduced.[114]

These provisions lacked much force until the 2000 Conference of the Parties to the CBD agreed to the specific terms of the Biosafety Protocol. The Protocol implements Articles 19.3 and 19.4 by granting countries the legal authority to deny the importation of any GMO or GMO-derived product if the country deems it a threat to public health or the environment. The criterion used to judge safety under the Protocol is an extremely expansive version of the precautionary principle.[115] Depending upon how it is interpreted and implemented, the Biosafety Protocol could have a significant impact on international trade involving many products of biotechnology. The richest potential source of the

[113] Biosafety refers to safeguards against the negative effects, either to humans, animals, or the environment in general, of genetically modified organisms (GMOs). Given trends in biotechnology, GMOs are likely to make up an increasing proportion of products derived from genetic resources collected by bioprospecting.

[114] *See* `http://www.biodiv.org/chm/conv/art16.htm` (2000).

[115] *See* `http://www.biodiv.org/biosafe/Biosafe-Prot.html` (2000).

genetic resources needed to create GMOs is biodiversity. Thus, the Biosafety Protocol has the potential to influence decisions regarding whether or not to invest in bioprospecting for novel genetic resources. Ironically, many of the countries who championed the Biosafety Protocol would also stand to gain most from increased bioprospecting for the genetic resources whose use the Protocol would restrict.[116]

Complete implementation of the provisions of the CBD relating to bioprospecting will likely take a many years, especially among less developed countries with weak institutional bases for legislation and enforcement.[117] Consequently, it is unclear how the above provisions will function in practice or interact with each other and with other sources of law. However, it is likely that the CBD will have a significant impact on bioprospecting.

Implementation

Since the CBD was opened for signatures in 1992, countries, government agencies, companies, and non-profit organizations have begun to implement the treaty. The provisions relating to the regulation of bioprospecting have received considerable attention. In order to provide an indication of how access agreements are being implemented, a number of examples are explored below.

[116] Personal communications from Wendy E. Franz, international environmental politics scholar in the Department of Government, Harvard University (2000).
[117] *See id.*

The Philippines is ideally suited to profit from the provisions in the CBD promoting equitable sharing of benefits from bioprospecting. It possesses one of the greatest concentrations of biodiversity on earth[118] as well as a legal structure to govern access to these resources. The Phillippines has erected a comprehensive procedure that firms interested in bioprospecting there must follow. The domestic legal basis for this procedure is the Philippines Executive Order 247 and Implementing Regulations that cover bioprospecting.[119] The following is a summary of how these regulations function in practice:

1 The applicant must submit a Letter of Intent and three copies of the Research Proposal to the Inter-Agency Committee on Biological and Genetic Resources (IACBGR) through the Technical Secretariat and pay a filing fee of P25[120].
2 The Technical Secretariat conducts an initial screening of the application to determine whether the research is within the coverage of the Executive Order.
3 If the proposed research is within the coverage of the Executive Order then: (a) the Technical Secretariat provides the applicant with a checklist of additional requirements to be submitted which include, among other things, (i) a properly completed application form, (ii) a profile of the organisation seeking access, (iii) an Environmental Impact Assessment, as determined by the Technical Secretariat, and (iv) the correct processing fee (P1,000 per application for a Philippine national, P2,000 for a foreign national)[121]; (b) the applicant submits a copy of the summary of the research proposal, duly certified by the Technical Secretariat, to the recognised head of the indigenous peoples, municipal or city mayor of the Local Governmental Unit, Protected Area Management Board, or private land-owner on whose land the bioprospecting is to take place for the required Prior Informed Consent Certificate[122].

[118] *See* Norman Myers, Russell A. Mittermeier, Cristina G. Mittermeier, Gustavo A.B. da Fonseca, and Jennifer Kent, *Biodiversity hotspots for conservation priorities*, 403 Nature 853-858 (2000).
[119] *See* Kerry ten Kate and Sarah A. Laird, The Commercial Use of Biodiversity - Access to Genetic Resources and Benefit-Sharing 18 (1999).
[120] P refers to Philippine Pesos: 1 Philippine Peso = 0.02443 US Dollar as of March 30, 2000; so, P25 = $0.61.
[121] These fees are equivalent to $24.43 for a Philippine national and $48.86 for a foreign national. *See id.*
[122] Prior informed consent refers to the consent obtained by the applicant from the Local Community, Indigenous Cultural Communities or Indigenous Peoples (IP), Protected Area

4 If the research proposal is not within the coverage of the Executive Order, the Technical Secretariat issues a Certificate of Exemption and refers the proposal to the government agency that has jurisdiction over the project.
5 The applicant submits the Prior Informed Consent Certificate signed by the recognised head of the indigenous peoples, municipal or city mayor of the Local Governmental Unit, Protected Area Management Board, or private land-owner concerned, together with proofs of public notification and sectoral consultation.
6 The Technical Secretariat conducts an intial review and evaluation of the application and documents.
7 The Technical Secretariat submits the results of its evaluation, including the draft Commercial Research Agreement, to the IACBGR within 30 days from receipt of all requirements.
8 The IACBGR conducts a final evaluation of the application.
9 The IACBGR submits its recommendation to the Agency concerned.
10 The Secretary of the Agency concerned considers the approval or disapproval of the Research Agreement.
11 Upon approval of the application, the applicant pays the bioprospecting fee as determined by the IACBGR.
12 The Agency concerned transmits the signed Research Agreement to the Technical Secretariat who then furnishes a copy to the applicant, indigenous peoples, local community, Protected Area Management Board, or private land-owner concerned.[123]

Clearly the process by which one gains legal approval for bioprospecting in the Philippines is lengthy and complicated. Prior informed consent can be required not simply from multiple governmental agencies but from multiple local stakeholders (e.g., indigenous peoples, private land-owners). Given the apparent necessity of securing such a sophisticated level of permission from so many actors, the potential for hold-out situations is significant at many stages of the approval process. Although the official application fees are *de minimus*[124], the total transaction costs of approval from all necessary parties, and the opportu-

Management Board (PAMB) or Private Land Owner concerned, after disclosing fully the intent and scope of the bioprospecting activity, in a language and process understandable to the community, and before any bioprospecting activity is undertaken., Philippines Implementing Regulations §2, reproduced in Kerry ten Kate and Sarah A. Laird, The Commercial Use of Biodiversity - Access to Genetic Resources and Benefit-Sharing 28 (1999).

[123] *See* Kerry ten Kate and Sarah A. Laird, The Commercial Use of Biodiversity - Access to Genetic Resources and Benefit-Sharing 30 (adapted from Box 2.6) (1999).

[124] They amount to less than $50. *See supra* note 110.

nity cost of time spent in that endeavor, is likely to be much greater.

The complexity and expense of navigating the Philippines' regulatory system has caused considerable concern among prospective commercial bioprospectors. Firms perceive its major shortcomings as including (1) excessive bureaucracy, (2) high financial costs of complying with detailed procedures, (3) inflexibility to the different requirements of individual firms, and (4) compulsory licensing of technology.[125] In fact, the perception of the Philippines' access system as overly burdensome has influenced at least some companies to forego bioprospecting there and instead to seek out more favorable terms of access to biodiversity elsewhere.[126] One source of these difficulties may be the failure by the Philippines government to involve industry in the drafting of regulatory procedures to implement Executive Order 247.[127] However, the Philippines government has responded by seeking input from parties potentially interested in conducting bioprospecting there, emphasizing that the access regulations are intended to be flexible, and attempting to improve their administration.[128] It remains to be seen whether these somewhat superficial reforms can attract a greater share of commerical bioprospecting to the Philippines.

Perhaps the most well known example of a legal regime governing access to biodiversity involves the National Biodiversity Institute of Costa Rica (INBio)[129].

[125] *See* Kerry ten Kate and Sarah A. Laird, The Commercial Use of Biodiversity - Access to Genetic Resources and Benefit-Sharing 294 (1999).
[126] *See id.* 301.
[127] *See id.* 294.
[128] *See id.*
[129] *See* INBio homepage (English version) at `http://www.inbio.ac.cr/en/default.html` (2000).

Established in 1989, well before the CBD existed, INBio's purpose is to enhance the benefits that accrue to Costa Rica from the use of its abundant biodiversity. Like the Philippines, Costa Rica contains a disproportionate share of the earth's biodiversity.[130] For many years it has been a popular destination for both academic scientists and commercial bioprospectors interested in studying and collecting its biodiversity, in part because of its stable political climate. However, recognition of the potential value of its biodiversity resources and disenchantment with its negligible share of the benefits derived therefrom led Costa Rica to pass Biodiversity Law 7788[131]. Costa Rica hopes to derive significant benefits from its biodiversity: Bioprospecting stands as the industry of the next century and Costa Rica has a unique opportunity to lead the process.[132]

INBio established the prototype for later access agreements when it concluded a commercial agreement to supply Merck & Company, Inc.[133], a large multinational pharmaceutical company, with 10,000 chemical samples from a variety of Costa Rican organisms in return for a $1 million payment, $130,000 worth of modern research equipment, and future royalties (at an undisclosed rate) on the total profits of any commercial product successfully developed from the INBio samples.[134] INBio's strategy is based on the development of a diversified portfolio of bioprospecting research agreements that foster innovation, learning and

[130] *See* Norman Myers, Russell A. Mittermeier, Cristina G. Mittermeier, Gustavo A.B. da Fonseca, and Jennifer Kent, *Biodiversity hotspots for conservation priorities*, 403 Nature 853-858 (2000).

[131] Article 63 of the Biodiversity Law specifically deals with issues of access to biodiversity.

[132] *See* `http://www.inbio.ac.cr/en/pdb/Prosp.html` (2000).

[133] *See* corporate homepage at `http://www.merck.com` (2000).

[134] *See* David R. Downes, *New Diplomacy for the Biodiversity Trade: Biodiversity, Biotechnology and Intellectual Property in the Convention on Biological Diversity*, 4 Touro J. Transnational Law 1-8 (1993).

local capacity building.[135] It has had considerable success in attracting parties interested in access to Costa Rican biodiversity and successfully negotiating access agreements.[136] Nevertheless, the total amount of direct revenue generated by these access agreements thus far has been modest;[137] indirect benefits, such as infrastructure, scientific and technical training, and development of legal expertise in negotiating favorable access agreements, are difficult to measure but may be significant. The perceived success of the INBio model for bioprospecting has even inspired Mexico to set up a similar institution, CONABIO, that has begun to attract commercial bioprospecting clients.[138]

Many other legal access regimes exist in addition to those set up by the Philippines and Costa Rica, though few are as comprehensive or well established.[139] Of particular note, however, is a regional agreement known as the Andean Pact Common Regime on Access to Genetic Resources. In 1996, Bolivia, Colombia, Ecuador, Peru and Venezuela successfully agreed to an common legal regime for granting access agreements for bioprospecting.[140] Among the motivations for a common regime was the desire to avoid unnecessary competition between

[135] *See* `http://www.inbio.ac.cr/en/pdb/Prosp.html` (2000).

[136] INBio has successfully concluded access agreements with Universidad de Costa Rica, Universidad Nacional, Escuela Agrícola de la Región del Trópico Húmedo (EARTH), Instituto Tecnológico de Costa Rica (ITCR), Strathclyde University, Düsseldorf University, Lausanne University, University of Massachusetts, Cornell University, Bristol Myers Squibb, Merck & Co., Ecos-La Pacífica, Indena, Givaudan Roure, Diversa, and other parties. *See* `http://www.inbio.ac.cr/en/pdb/Prosp.html` (2000).

[137] *See* `http://www.inbio.ac.cr/en/pdb/Prosp.html` (2000). (From an strict economic point of view, since INBio started this activity in 1991, direct financial contributions to other divisions in INBio, the Conservation Areas, MINAE and national universities exceed $2.5 million dollars.).

[138] *See* Harvey Bialy, *A new look in North-South biopartnerships*, 16 Nature Biotechnology 986 (1998).

[139] *See* Kerry ten Kate and Sarah A. Laird, The Commercial Use of Biodiversity - Access to Genetic Resources and Benefit-Sharing 16 (1999). (The authors report 40 countries, and several subnational jurisdictions, with access and benefit-sharing measures at various stages of development).

[140] Officially called The Acuerdo de Cartagena.

these similarly situated and richly biodiverse[141] countries in trying to attract commercial bioprospecting: establishing a region-wide access and benefit sharing regime makes it more difficult for bioprospectors to play one country off against its neighbours to secure overly favourable conditions.[142] Under the common regime, access agreements are negotiated by each national government but must conform to the same general rules. To obtain access an application must be submitted along with a project proposal and detailed request form.[143] The request form requires specific information regarding the nature of bioprospecting activities contemplated by the applicant:

1 identification and legal status of the institution,
2 identification of the genetic resources provider or source, including the associated intangible components, if applicable,
3 identification of the researcher or national organization,
4 identification and curriculum vitae of the project director and counterparts,
5 a list of the activities to be carried out, and
6 the locality where the research project will take place, including exact coordinates.[144]

Although the avowed purpose of the The Andean Pact access regime is to increase the benefits from bioprospecting that accrue to the countries in which biodiversity samples are collected, it is likely to be greeted by industry negatively as overly burdensome, just as the Philippines' access regime has been.[145] On

[141] *See* Norman Myers, Russell A. Mittermeier, Cristina G. Mittermeier, Gustavo A.B. da Fonseca, and Jennifer Kent, *Biodiversity hotspots for conservation priorities*, 403 Nature 853-858 (2000).
[142] *See* Graham Dutfield, *The Andean Pact Common System on Access to Genetic Resources: A Commentary*, `http://users.ox.ac.uk/~wgtrr/andpacomm.htm` (1997).
[143] *See* Raul O. Castillo, The Andean Common Code for the Access to Genetic Resources: A General Overview in Global Genetic Resources: Access, Owneship, and Intellectual Property Rights (Eds. K. Elaine Hoagland and Amy Y. Rossman) 300 (1997).
[144] *See id.*
[145] *See* Kerry ten Kate and Sarah A. Laird, The Commercial Use of Biodiversity - Access to Genetic Resources and Benefit-Sharing 32 (1999).

the other hand, the Andean Pact countries do have the distinct advantage of containing a disproportionate amount of the biodiversity resources on earth[146], which should enhances their attractiveness to bioprospectors. However, there is insufficient data as yet to conclude whether commercial bioprospecting will avoid Andean Pact countries in favor of those with more accommodating access regimes or accept more stringent terms of access in return for higher likelihoods of bioprospecting success.

Regional access regimes similar to the Andean Pact regime may become more common. In 1998, the governing council of the Organization of African Unity (OAU)[147] approved a model bill designed to regularize legal access regimes across the continent as well as to secure ownership of intellectual property rights for indigenous local communities.[148] There is a lot of animosity towards bioprospecting throughout Africa based on perceptions of historical inequities: The opposition is based partly on memories of colonial times, when areas of the continent were used as a free source of plants by staff from colonial powers' botanic gardens.[149] The model bill is aimed particularly at 'bioprospecting' by multinationals.[150] As with the Andean Pact regime, a primary motivation for a pan-African legal access regime is to ensure that the maximum amount of benefits from bioprospecting redound to Africans; a common regime is seen as a

[146] *See* Norman Myers, Russell A. Mittermeier, Cristina G. Mittermeier, Gustavo A.B. da Fonseca, and Jennifer Kent, *Biodiversity hotspots for conservation priorities*, 403 Nature 853-858 (2000).

[147] *See* organization homepage (with membership list) at `http://www.oau-oua.org` (2000). (The OAU has 53 member states.).

[148] *See Africa seeks to assert rights to 'natural' drugs*, 394 Nature 9 (1998).

[149] *See* Ehsan Masood, *Old scores surface as African states face new opportunities*, 392 Nature 540 (1998).

[150] *See* Ehsan Masood, *Africa defends rights to indigenous knowledge*, 392 Nature 423 (1998).

means of avoiding a counterproductive race-to-the-bottom in access standards. Conditions may be particularly favorable in Africa for agreeing to a model bill because of the relative importance bioprospecting already has there: This debate is particularly significant in Africa, where phytomedicine is an integral part of traditional medical practice, and where it is estimated that up to 80% of the population resort to traditional medicine for their health needs, including those who also visit modern health facilities.[151] The tremendous wealth of biodiversity in Africa[152] coupled with its very low level of economic development may also provide impetus to a common access regime. An access regime common to an entire continent would likely have a global impact on the practice of bioprospecting.

It is difficult to draw general observations based on the very limited number of access agreements that have been implemented thus far. However, what limited evidence there is suggests two conclusions. First, countries that insist on cumbersome and inflexible terms of access (e.g., the Philippines) have not been as successful in attracting commerical bioprospecting as have countries who offer more flexible and cooperative terms (e.g., Costa Rica, Mexico). Second, legal access regimes are increasingly being contemplated at the regional, rather than national, level.

Technological Challenges

[151] *See* Lydia Makhubu, *Bioprospecting in an African Context*, 282 Science 41 (1998).

[152] *See* Norman Myers, Russell A. Mittermeier, Cristina G. Mittermeier, Gustavo A.B. da Fonseca, and Jennifer Kent, *Biodiversity hotspots for conservation priorities*, 403 Nature 853-858 (2000).

From the soon-to-be-completed Human Genome Project to combinatorial chemistry, scientific advances are poised to revolutionize drug discovery and even health care.

- Special Report on Drug Discovery in Science[153]

Two technologies developed in the late 1990s promise to have a profound impact on the development of new drugs: genomics[154] and combinatorial chemistry[155]. Both hold the potential systematically to alter the usefulness of biodiversity for drug discovery. However, it is unclear as yet whether this alteration in value is likely to be upwards or downwards.

The nascent discipline of genomics accelerated rapidly during the 1990s due to a variety of developments. The Human Genome Project (HGP) was established in 1990 to find the estimated 100,000 or more human genes and determine the sequence of the 3-billion DNA basepairs.[156] Among it many effects, the HGP accelerated the development of new technology able to sequence DNA more quickly and efficiently. In the ensuing years, these improvements have allowed the complete sequencing of the genomes of more than 20 species.[157] Furthermore, a

[153] *See* Julia Uppenbrink and Jeffrey Mervis, *An Information Revolution - Introduction*, 287 Science 1951 (2000).

[154] The study of genomes, which includes genome mapping, gene sequencing and gene function., *See* Life Science Dictionary, Biotech Resources and Indiana University `http://biotech.icmb.utexas.edu/search/dict-search.phtml?title=genomics` (2000).

[155] A combinatorial chemist, or chemical geneticist, synthesizes vast numbers of small molecules (using a strategy named split-and- pool synthesis), chooses from the myriad of methods to synthesize complex, asymmetric, natural product-like molecules, and selects the desired ligands through the use of screens compatible with the split-and-pool method of small molecule generation. *See* Stuart Schreiber (Morris Loeb Professor of Chemical Biology in the Department of Chemistry and Chemical Biology at Harvard University) lab group website `http://www-schreiber.chem.harvard.edu/home/research.html` (2000).

[156] *See* Human Genome Project website at `http://www.ornl.gov/TechResources/Human_Genome/hg5yp` (2000).

[157] These include: *Mycoplasma genitalium*, *Rickettsia prowazekii*, *Haemophilus influenzae*, *Methanococcus jannaschi*, *Bacillus subtilis*, *Escherichia coli*, *Saccharmomyces cerevisiae*,*Caenorhabditis elegans*, and *Drosophila melanogaster*. *See* Benjamin Lewin, Genes VII 75 (2000).

commerical biotechnology firm, Celera Genomics[158], recently announced that it had completed sequencing more than 90% of the human genome and identified more than 97% of human genes[159]; the company expects to complete the entire human genome in 2000, three years ahead of the HGP.

Genomics should provide a powerful means for developing drugs. Instead of approaching drug design as the application of external chemicals (many of them natural products or products derived therefrom), drugs will be based on an understanding of how genes, proteins, and the cells that house them, behave. This approach is often called rational drug design. The technique has already demonstrated its advantages in the development of novel antibiotics:

> Traditionally, antimicrobial drug discovery has relied upon random screening or semi-rational modification of known structural series. These strategies have failed to deliver sufficient molecular diversity to counteract the contstant selection pressures within the clinic, resulting in substantial and increasing drug resistance... The new technologies based upon microbial genomics not only provide the tools to drive target discovery beyond established biochemistry but also create the ability to compare targets for likely performance in a clinical situation. The technologies are not limited to target selection and are providing new approaches to support compound optimization into early drug development. This not only streamlines accurate compound evalutation but also converts random screening campaigns into rational compound optimizations, thus revolutionizing both antibacterial and antifungal drug screening. We can thus expect a whole variety of novel agents with new mechanisms of action, of unrelated structural classes, to be generated from increasingly efficient drug-hunting programs.[160]

An additional advantage of a genomic approach may be the ability to tailor the design and application of drugs to the specific characteristics of an individual's genes:

> Imagine the benefit to the development of new therapies if drugs entering

[158] *See* Celera Genomics homepage at `http://www.celera.com` (2000).
[159] *See* `http://www.pecorporation.com/press/prccorp011000.html` (2000).
[160] *See* John Rosamond and Aileen Allsop, *Harnessing the Power of the Genome in the Search for New Antibiotics*, 287 Science 1973 (2000).

clinical trials are almost ensured to be well tolerated in the body and to have the desired effect. Or imagine relatively short clinical trials, confirmatory final tests to guarantee that drugs and diagnostics are safe and effective.[161]

In short, genomics is likely to revolutionize the design of new drugs. But how will genomics effect bioprospecting?

Some have suggested that genomics heralds the decline of bioprospecting by reducing the need for natural products in drug hunting.[162] However, even if the demand for natural products were to be reduced, the demand for what the CBD calls genetic resources[163] is likely to increase:

> Where past bioprospecting activity has concentrated on the collection and identification of natural chemicals which organisms may use to protect themselves against predators or disease, the emphasis in future will be on the collection of genetic information from exotic species, for possible application in both genetic medicine and genetic engineering of crops.[164]

So powerful is the view that the genetic component of biodiversity is economically valuable that Celera Genomics recently amended its business plan (that is, to become the definitive source of genomic and related agricultural and medical information[165]) to include the sequencing of other species in addition to the human.[166] In short, genomics would seem to hold the potential to enhance the value of the genetic component of biodiversity by making its extraction and manipulation much more efficient and less expensive.

[161] *See* Chris Sander, *Genomic Medicine and the Future of Health Care*, 287 Science 1977 (2000).
[162] *See* Colin Mcilwain, *When rhetoric hits reality in debate on bioprospecting*, 392 Nature 537 (1998).
[163] *See, e.g.*, CBD Article 1 `http://www.biodiv.org/chm/conv/art1.htm` (2000).
[164] *See* Colin Mcilwain, *When rhetoric hits reality in debate on bioprospecting*, 392 Nature 535 (1998).
[165] *See* `http://www.pecorporation.com/press/prccorp011000.html` (2000).
[166] *See, e.g.*, `http://www.pecorporation.com/press/prccorp011000.html` (2000) (Announcing the planned sequencing of the house mouse (*Mus musculus*) genome after completion of the fruit fly (*Drosophila melanogaster*) and human genomes).

Even more than genomics, combinatorial chemistry has been heralded as eliminating the need for natural products yielded by bioprospecting.[167] After all, the technique offers a powerful and highly efficient means of synthesizing large numbers of small molecules[168] that can be screened for efficacy as drugs.[169] However, despite its tremendous promise, the view that it will completely replace natural products is exaggerated because combinatorial libraries[170] are usually generated using natural products as templates.[171] Furthermore, the perceived failure of combinatorial chemistry to yield successful drugs may be spurring a renaissance in bioprospecting for natural products:

> . . . drug discovery is on a back-to-nature trip. In the past two years, scores of small companies have set up alongside the major pharmaceutical firms to find and screen chemical compounds from hundreds of thousands of plants and micro-organisms. . . combinatorial chemistry is limited by the imaginations of the chemists who do it, and the range of chemical reactions they can devise. As a result, its products frequently fail to pass laboratory tests for biological function. In contrast, nature's molecules have already proved their usefulness in the ultimate screening programme: over three and a half billion years of evolution.[172]

In reality, it is unlikely that either approach - bioprospecting for natural products or combinatorial chemistry - will alone be sufficient in the near future. Rather, they will often be used in tandem:

Most natural products researchers feel that natural products and combina-

[167] *See* Colin Mcilwain, *When rhetoric hits reality in debate on bioprospecting*, 392 Nature 535 (1998).

[168] *See Biotech's secret garden*, The Economist (May 30 U.S. Edition) 75 (1998). (up to 40,000 separate compounds in a single experiment.).

[169] *See generally* Stuart L. Schreiber, *Target-Oriented and Diversity-Oriented Organic Synthesis in Drug Discovery*, 287 Science 1964-1968 (2000).

[170] The collection of distinct chemical species generated by combinatorial chemistry.

[171] For example, in the context of protein dimerization: Thus far, with only few exceptions, the ligands used have been either natural products or their synthetic variants (e.g., synthetic dimers of natural products). *See* Stuart Schreiber (Morris Loeb Professor of Chemical Biology in the Department of Chemistry and Chemical Biology at Harvard University) lab group website at `http://www-schreiber.chem.harvard.edu/home/research.html` (2000).

[172] *See Biotech's secret garden*, The Economist (May 30 U.S. Edition) 75 (1998).

torial chemistry are complementary approaches to drug discovery, with combinatorial chemistry providing large quantities of similar compounds, and natural products providing diversity.[173]

However, as techniques and technology improve, combinatorial chemistry would seem to represent a medium to long term threat to bioprospecting for natural products, particularly as the *de novo* design of templates (a major goal of the next generation of combinatorial chemistry techniques) becomes more feasible and begins to replace natural product templates.

Both genomics and combinatorial chemistry offer great improvements in the design of new drugs. However, neither approach is likely to replace bioprospecting in the near future. In fact, the potential exists for the commercial value of biodiversity to be enhanced as aspects of it (especially genetic resources) become more easily isolated and manipulated for the design of new drugs.

Conclusion

Bioprospecting has historically been a dominant source for medicines and agricultural products. It remains a significant source for these, and a variety of other, economic goods. In the developing world, the vast majority of the population regularly relies on natural products as their main source of medicine. Even in the developed world, a majority of the most-prescribed prescription drugs are either natural products themselves or substantially derived therefrom. Genetic

[173] *See* Kerry ten Kate and Sarah A. Laird, The Commercial Use of Biodiversity - Access to Genetic Resources and Benefit-Sharing 57 (1999).

resources represent a rapidly growing and highly promising source of new drugs, agricultural products, and other fruits of biotechnology.

The economic value of the products derived from biodiversity (e.g., as a source for the development of new drugs) is difficult to assess. A first order approximation, based on the value of genetic resources alone, indicates the possibility that biodiversity has high economic use value. Theoretical economic estimates of biodiversity's value for drug development range from negligible to relatively high. Estimates of sales of perscription drugs made or derived from natural products are relatively large; when combined with agricultural products similarly derived, the estimated economic use value of biodiversity becomes quite large.

The Convention on Biological Diversity, introduced in 1992 at the United Nations Conference on Environment and Development, represents a landmark attempt to establish an international legal framework for the comprehensive conservation of global biodiversity. It recognizes national sovereignty over biodiversity and promotes the fair and equitable sharing of the benefits that flow from that resource. The CBD contemplates that such benefits will be generated by natural products and genetic resources collected through bioprospecting and developed into commercial products like drugs and crops.

A growing number of countries have begun to implement the CBD by establishing legal regimes governing access to their biodiversity resources. The Philippines has established a strict and complicated access regime that is regarded by potential commercial bioprospectors as excessively onerous. In contrast,

Costa Rica and Mexico have set up a flexible access regime that encourage bioprospecting agreements as potential sources of revenue, equipment modernization, and expertise development. They have successfully developed partnerships with commercial bioprospectors and have received both modest remuneration and the promise of future royalties on successful commercial products developed from their biodiversity. Initial indications suggest that flexible legal access regimes are more successful in attracting bioprospecting clients.

The Andean Pact Regime may signal a trend towards the establishment of regional bioprospecting access regimes, established in part to prevent unnecessary competition between neighboring countries to attract commercial bioprospecting. The Organization of African Unity is currently negotiating a legal access regime that is similar in nature, but on the much grander scale of a whole continent. The Andean Pact and OAU may herald a trend towards the regionalization of legal access regimes for bioprospecting.

New technologies such as genomics and combinatorial chemistry may represent challenges to the importance of bioprospecting. However, they could enhance the importance of biodiversity. Genetic resources may provide an important source of raw material for biotechnology and natural products may provide needed templates for the generation of synthetic combinatorial libraries. In any case, neither technology is likely to eliminate the need for bioprospecting in the short term.

From new drugs to improved crop strains, biodiversity remains vitally important to human health and welfare. If the Convention on Biological Diversity

is implemented in a manner that maximizes the benefits from biodiversity and equitably shares them with source countries, there will exist a substantial incentive to conserve biodiversity. To fulfill these objectives, source countries must design legal access regimes flexible and efficient enough both to encourage continued bioprospecting and to derive sufficient benefits from it and prospective bioprospectors must be will to negotiate and act in good faith.