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An Overview of Bioprospecting and the *Diversa* Model

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Implementing the Principles of the United Nations Convention on Biological Diversity: The Experience of Kina Biotech in Peru

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Bioprospecting Partnerships In Practice: A Decade of Experiences at INBio in Costa Rica

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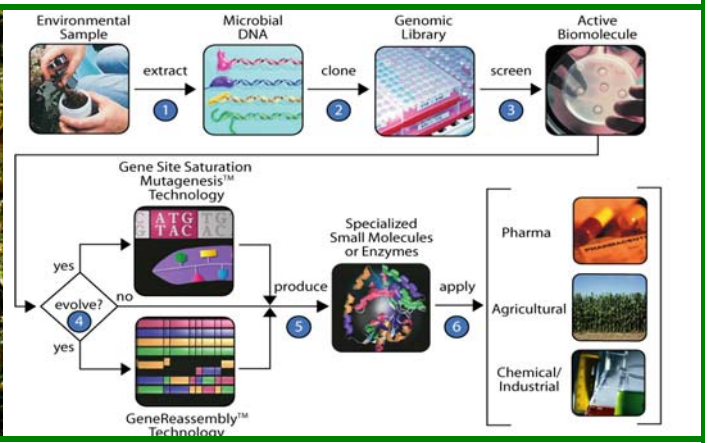

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Contents

An Overview of Bioprospecting and the *Diversa* Model [1]

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Executive Summary

Overview—The planet's vast and mostly unexplored microbial resources hold immeasurable potential. Microbial biodiversity is the basis for many natural discovery programs seeking novel compounds for use in pharmaceuticals, agriculture, and other industrial applications. As technology continues to find new ways to access and explore these resources, governments, institutions, and private companies are working together to conserve, develop products from, and sustain the use of microbial biodiversity. To ensure the sustainable use of biodiversity, the value of establishing unambiguous property rights and clear benefit-sharing agreements in bioprospecting collaborations cannot be overestimated.

This paper discusses some of the economic and business concepts necessary in establishing mutually beneficial, successful, and sustainable partnerships between private enterprises and biodiversity providers. The paper also offers an example of one company's approach to creating biodiversity collaborations with various countries based on adherence to international guidelines for biodiversity, the establishment of clear intellectual property rights (IPRs), and equitable benefit-sharing. Finally, it provides a case study of a biodiversity collaboration between a private biotechnology company and several biodiversity-provider institutes in Russia.

International Guidelines—The Convention on Biological Diversity (CBD) and the Trade Related Aspects of Intellectual Property (TRIPS) agreement provide guidance on the protection and sustainable use of biodiversity. This general guidance, however, is not sufficient to answer all the relevant questions when crafting a biodiversity access agreement. Such an agreement sets out both the specific conditions of cooperation and a scheme for sharing the benefits resulting from cooperation.

Two key issues in designing biodiversity access agreements are property rights and the valuation of the biodiverse resource. The CBD establishes that property rights for biodiversity belong to the sovereign nation that houses them. Valuation, on the other hand, must be determined by the parties to the agreement and governed by the reality that the market sets the natural limit to the divisible monetary benefits. It should also be remembered that there are myriad non-monetary benefits that can be as valuable to the partners as the monetary ones.

Diversa's Approach—In addition to these international guidelines, Diversa Corporation, a biotechnology firm located in San Diego, CA, has developed and refined a set of principles for selecting partners and for creating agreements to help ensure long-term relationships based on the sustainable use of genetic resources. Through its patented technologies, Diversa can rapidly and efficiently identify target substances from environmental samples to discover novel gene products. Seeking sound collaborators with strong scientific qualities and access to unique biotopes and habitats, Diversa follows CBD guidelines and leads global corporate efforts to meet CBD goals.

When exploring options for new biodiversity collaboration, Diversa's first step is to conduct an assessment of countries based on their legal framework, political will, strength of potential partners, and the presence of unique and protected habitats. After identifying the country of interest and the institutional candidate, Diversa employs a bioprospecting framework developed over the past decade to help guide the structuring of the collaboration agreement. This framework has evolved significantly both through the implementation of biodiversity collaborations and through monitoring and adapting to changes within international conventions, such as the CBD.

As a result of Diversa's biodiversity collaborations, it has established a global network of partners providing access to a wide array of diverse ecosystems and habitats. This diversity has generated vast environmental libraries, products, and a robust product pipeline. Diversa's partners have also benefited from the collaborations, receiving more than USD 2 million in financial payments and USD 2 million in third-party grants to support their work with Diversa. In addition, Diversa has trained more than 100 scientists worldwide, improved infrastructure and scientific capacity, and has even helped individual scientists further their college and postgraduate studies.

Bioprospecting Case Study—Diversa's collaboration with the Russian Federation provides one example of the successful application of its principled approach to bioprospecting. Since 2000, Diversa has collaborated with four Russian government institutes through the United States Department of Energy *Initiatives in Proliferation Prevention* Program. Diversa and its Russian partners have benefited from not only the exchange of products but also from the transfer of technology and the education of scientists.

This case study on the partnership between Diversa and the Russian Federation demonstrates that successful biodiversity collaborations can result from principled approaches; moreover, these collaborations evolve not only through training and technology transfer but also through the working relationships that they foster over time.

1. Introduction

The value of establishing unambiguous property rights and clear benefit-sharing agreements in commercial partnerships based on biodiversity cannot be overestimated. Microbial biodiversity is an excellent source of the novel compounds used by many industries such as pharmaceuticals, agriculture, and chemicals. This paper discusses some of the economic and business concepts necessary for establishing mutually beneficial, successful, and sustainable partnerships between private enterprises and the owners of biodiverse resources. The paper also provides an example of one company's approach to creating biodiversity collaborations with various countries, an approach based on adherence to international guidelines for biodiversity, the establishment of clear IPRs, and equitable benefit-sharing. (The company, the Diversa Corporation, is a publicly traded American biotechnology company whose business involves the discovery and evolution of novel genes and genetic pathways from unique environmental sources.) In this context, biodiversity collaborations are agreements involving access to a unique biotope for bioprospecting. In addition, this paper presents a case study of a biodiversity collaboration between Diversa and several state laboratories in the Russian Federation.

2. Overview of Key International Conventions and Agreements

Governments that recognize the need to protect inventors, encourage innovation, and disseminate knowledge have long acknowledged IPRs. Biodiversity holds tremendous social, economic, and other values. It thus highlights the need for international agreement on IPRs, particularly the importance of these agreements for sustainable use. The current trend towards global harmonization of the IP system appears to support and encourage the continued collaboration between the private sector and the owners of genetic resources. The Convention on Biodiversity (CBD) and the Trade Related Intellectual Property Rights Agreement (TRIPS) are the two main international conventions that provide guidance on the conservation and sustainable use of biodiversity and the standard application and enforcement of IPRs, respectively (for a discussion on biodiversity and IPRs, see WWF/CIEL 2001).

2.1 The Convention on Biological Diversity

One of the focal agreements of the 1992 Earth Summit in Rio de Janeiro was the CBD, a non-binding international agreement with three main goals:

- conservation of biodiversity;
- sustainable use of the components of biodiversity; and
- fair and equitable sharing of the benefits from the use of genetic resources.

With the shared goal of sustained development and protection of the global environment, all signatories to the CBD have committed to conservation and the sustainable use of biodiversity. Additionally, all have committed to exploring this diversity and equitably sharing the benefits that may arise from such exploration. The CBD recognizes a government's national sovereignty over all genetic resources within its borders (Article 15) and provides that access to these resources be carried out on "mutually agreeable terms" subject to the "prior informed consent" of the country of origin.

The recent adoption of the Bonn Guidelines Decision VI/24 by the Parties of the CBD during the sixth meeting of the Conference of the Parties (COP VI) marked an important new development in the creation of legal frameworks and effective management of bioprospecting activities in provider countries. Decision VI/24 addressed access to genetic resources and the fair and equitable sharing of the benefits arising from their utilization. This decision is widely recognized as an important first step in an evolving

process through which Parties will fulfill their commitments under the CBD. Parties now have good access and benefit-sharing reference resources to help them develop their respective legislative, administrative, or policy measures and to identify key components of the bioprospecting agreements that correspond to their needs and interests.

Issues that are not addressed effectively by the Bonn Guidelines and still require further analysis and debate within the CBD concern traditional knowledge and technology transfer. The Conference of the Parties at its seventh meeting, in decision VII/19, addressed the Bonn Guidelines under section A. The COP recognized "that the Guidelines are making a useful contribution to the development of national regimes and contractual arrangements for access and benefit-sharing and to the implementation of the objectives of the Convention."[3]

2.2 Trade Related Aspects of Intellectual Property Rights (TRIPS)

The 1994 Trade Related Aspects of Intellectual Property Rights (TRIPS) agreement among countries in the World Trade Organization covers all the main areas of IP, including the establishment of standards for enforcement and protection, and a system for dispute resolution. By identifying minimum IP legislation standards, the agreement provides potential investors with a basic framework within which to operate. With respect to this paper's concerns, it is also important to note Article 7 of the agreement,[4] which states that the protection and enforcement of IPRs should contribute to:

- promotion of technological innovation and the transfer and dissemination of technology;
- mutual advantage of producers and users of technological knowledge that is conducive to social and economic welfare; and
- a balance of rights and obligations.

The main goals of the CBD and TRIPS, applied to microbial biodiversity, are to provide general guidance for parties when developing agreements for access to these resources. It is important to realize, however, that these conventions are agreements on broad standards of conduct that provide overarching principals but do not provide instructions to meet the requirements of every unique situation. Case studies also illustrate how similar situations may have been handled in the past. Yet, from the perspective of two parties attempting to come to an agreement on obtaining/providing access to a microbial resource that may or may not become a successful commercial product, the international agreements and case studies may leave many questions unanswered. Therefore, in addition to relying on international guidance and lessons learned, parties must also use common sense to strike a balance between protecting rights and providing fair compensation on the one hand, and working within limits imposed by markets on the other.

3. Microbial Biodiversity

3.1 What is Microbial Biodiversity?

Microbes, including bacteria, archae, and fungi, are the world's most genetically diverse organisms. Indeed, these prokaryotic domains and lower eukaryotes house the vast majority of phylogenetic and metabolic diversity and are found in every ecosystem (Figure 1).

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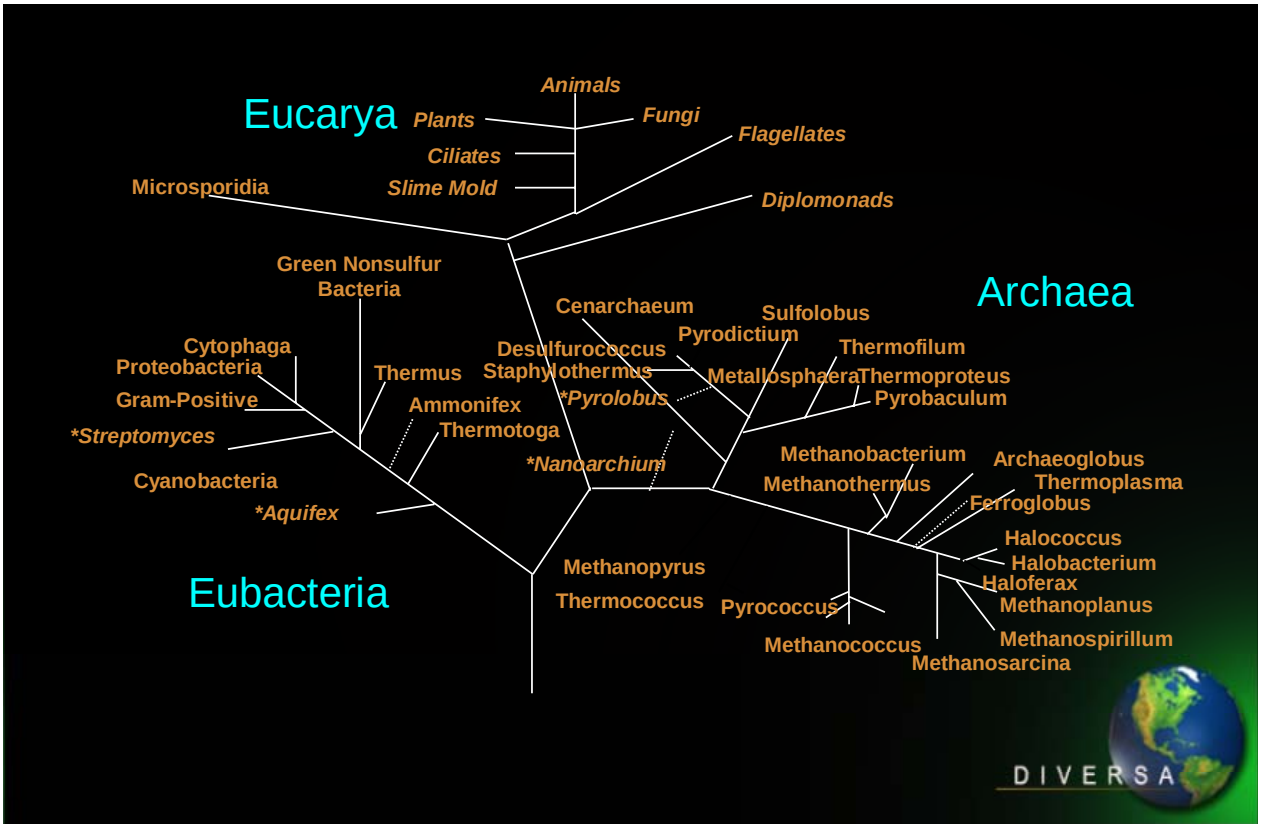
[3] www.biodiv.org/programmes/socio-eco/benefit/bonn.asp

[4] www.wto.org/english/docs_e/legal_e/27-trips.pdf

Figure 1: Microbial Genomics—The Tree of Life



Through billions of years of natural selection in dissimilar environments, microbes have developed broader and more varied characteristics than those observed in plants or animals. The uniqueness of many of these microbes enables the existence and evolution of larger flora and fauna that have been traditionally preserved under biodiversity efforts. In addition to silently enabling and supporting life for larger plants and animals, microorganisms have already been proven to hold the keys to advances in human health, improvements in industrial processes, and a variety of other beneficial applications.

Often the microorganisms found in extreme environments, extremophiles, provide the diversity required for these applications. The microbes are found in forbidding environments where little else lives, in such diverse and harsh environments as the thermal vents at the bottom of the Atlantic Ocean, the bellies of termites in Costa Rica, translucent stones in the dry desert valleys of Antarctica, and soils contaminated with polychlorinated biphenyls (PCBs) in Russia. Because of their ability to live in harsh environments, extremophiles are increasingly used in industrial processes.

3.2 Microbial Biodiversity and Technology

Recent advances in biotechnology allow target compounds from environmental samples to be identified much more rapidly. Traditionally, microorganisms are isolated and cultured in laboratories, a process that requires scientists to recreate the environments in which the target microbe lives. Partly because extreme environments are too difficult to replicate in the laboratory, many of these microorganisms remain unstudied. It is estimated that only approximately 1% of the world's billion plus microbial species have been studied (Marshall 2000; see also Table 1).

Table 1: Microbial Challenge

Habitat	Cultured (%)
Seawater	0.001-0.1
Freshwater	0.25
Soil	0.3
Activated Sludge	1.0-15.0

Source: Amann *et al.* 1995.

A genomic approach pioneered by Jay M. Short and coworkers at the Diversa Corporation is not only faster but can also provide access to more (by many orders of magnitude) microorganisms than is possible through traditional culturing, as shown in Table 2. This genomic approach, in which DNA is isolated directly from environmental samples without culturing, holds the promise of accessing a larger percentage of microorganisms currently unavailable.

Table 2: The Traditional vs. Genomic Approach

	Traditional Approach	Genomic Approach
Methodology	Culturing	Direct DNA Isolation
Characteristics	Slow and Limited	Fast and Novel
Results	10^4 Organisms	> 2 X 10^6 Genomes

3.3 Microbial Biodiversity as an Asset

Given the benefits provided by microbes known to us, if we speculate about the unlocked economic and scientific potential of the 99% of unstudied microbes, it is clear that this rich diversity has enormous value (even more value is created due to their constant and rapid evolution). Because of the vast potential that microbial biodiversity holds, its preservation and sustainable use seem a foregone conclusion. But in the case of biodiverse resources, "the absence of apparent value combined with absent or poorly defined property rights creates a problem of over exploitation and unregulated use" (OECD 2002). This statement underscores two problems that are as important to a single biodiversity collaboration as they are to the global community concerned with the preservation of biodiversity: property rights and valuation.

3.4 Microbial Biodiversity Ownership Rights

As noted above, the CBD is a point of departure for establishing the ownership rights of biodiversity, and by extension, microbial biodiversity. Significantly, the CBD establishes that countries have sovereign rights over the biodiversity resources within their borders. However, it is not within the competence or scope of this paper to debate the ownership of genetic resources. A large body of information written on property rights and IPRs and their application to genetic resources and genetically-derived products already exists (WWF/CIEL 2001). For any party involved in a biodiversity collaboration, establishing clear property rights is critical as a basis for the legal use of the resources and the sharing of benefits based on the use of the resource.

In practice, companies generally have to negotiate with a country's government to secure access to and use of microbial biodiversity. Yet, it is very important that parties understand that while a country has

the right to grant access and permission to use the resource, there can be many stakeholders affected by a biodiversity collaboration, including stakeholders that may not fall within the borders of the country in question. The parties must practically and responsibly consider how all stakeholders may be affected and assess whether they are entitled to benefits and should be included in the benefit-sharing agreement. An important factor in this regard is traditional use of lands/resources versus formal property rights. While countries own genetic resources, stewards of the resource are often local or indigenous communities that have traditionally used the land on which the resources are located for hundreds if not thousands of years. Although some of Diversa's partners work with indigenous communities, its model does not incorporate traditional knowledge because of its high throughput technology and focus on microorganisms as opposed to plants. Countries may not be able to achieve their goals of sustainable use of the resource if conflicts between traditional land tenure and legal property rights of genetic resources are not resolved (Tides Center/Biodiversity Action Network 1999).

Beyond ownership of *in situ* resources, parties must also determine who owns the results from the use of the microbial resource. This aspect must be considered by the parties to the agreement on a case-by-case basis. Ownership rights to the results will be part of the access agreement and will be reflected by the choice of benefit-sharing mechanisms employed in the agreement.

3.5 Microbial Biodiversity Valuation

Much has been written on valuation techniques for biodiversity (OECD 2002). Biodiversity has many values to different stakeholders. For instance, stakeholders can value the current use (use value), the future use of the biodiversity (option value), the availability of this asset in its natural state to pass to future generations (bequest value), and other values such as those related to the environment, climate, and the recreational, spiritual, and aesthetic aspects of the resource. This paper does not treat the comprehensive valuation of biodiversity. Rather, it addresses biodiversity valuation in the context of an input to the commercialization of microbial biodiversity and looks at options available for sharing benefits. Both of these issues are ultimately the responsibility of the parties entering into a biodiversity collaboration and would be reflected in a biodiversity access agreement between them.

As companies and countries cooperate on biodiversity, they enter into agreements that define a regime for sharing the benefits resulting from the use of biodiversity. This requires the appropriate valuation of the genetic resource as an input into the production of a product. In addition to access, significant value-added processing is required to transform the microbial biodiversity into a marketable product. The simplistic formula below grounds biodiversity collaboration with the private sector to its primary motivation to enter into such an arrangement, i.e., the market.

4. Resource + Value-Added Processing + Demand-Driven Component = Market Value of Product

Simply stated, the market value and the related monetary benefits of products resulting from biodiversity collaboration depend on the contribution of the microbial resource and the value-added processing, as well as the demand that transforms the resource into a finished product. (Non-monetary benefits are addressed below.) Biodiversity resource suppliers will demand benefits from those adding value, since they are the ones ultimately responsible for producing and marketing the product, which in turn generates the monetary value to be shared by both parties. It is important to note that while the partners may be flexible in determining the relative values of their contributions to the production process, ultimately only the market can determine the value of the resultant product. The market value of the product, therefore, as expressed in monetary terms, is the natural limit to the monetary value placed on

biodiversity resources. This directly impacts the amount of acceptable effort required to transform them into products. Accordingly, parties must be realistic about the relative values of their contributions to the product or risk rendering a potential collaboration uneconomic by creating costs that exceed potential benefits. The parties must understand that the monetary benefits to be shared are finite, may not be realized immediately, and may require significant, long-term investment. They must also realize that, since nucleic acid is forever evolving, genetic diversity is not finite. It is imperative that the parties to the agreement understand the panoply of benefit-sharing mechanisms at their disposal, both monetary and non-monetary, when crafting the initial access agreement.

The task of valuing the inputs to this process must be conducted on a case-by-case basis. Since no formula can hope to capture all variables, the parties themselves must be aware of the real costs and benefits associated with the project to ensure an equitable distribution of benefits.

When determining each party's requirements for entering an agreement, the following items merit consideration:

4.1 Valuation of the biodiverse resources

- Current uses (opportunity cost):[5] Does the proposed use of the resource interfere with another current use? What other possible uses for that resource would be abandoned by providing access to those wanting to add value? Are those values captured in the calculus for valuing the resource?
- Impact on the resource: Does the proposed use of the resource change the resource? Will the use lead to loss of biodiversity? Will use today prevent use by future generations (sustainability)?
- Protection of the resource: If this resource came from a national park or private reserve, then are the proportional costs associated with that protection taken into account? If so, how much of that effort (number of years multiplied by an average annual budget for that period) contributes to the quality of that resource (habitat)?
- Uniqueness of the resource: Can this resource be found in other countries or other jurisdictions? If so, how common is it to the region, continent, or world?
- Exclusivity of access to the resource: Does use of the resource by one company preclude use by other companies? Does use of the resource by one company preclude use for other purposes?

4.2 Valuation for adding value

- Sample collection: Who will conduct sampling? How will it be valued?
- Sample purification: Who will purify the sample into pure chemical extracts? As in the case with Diversa, who will extract the microbial DNA and RNA from the environmental sample? What methods will be used to maximize the yield of nucleic acid extracted from the environmental sample?
- Screening preparation: Who will prepare the pure chemical extracts or the nucleic acid into a platform that can be used for screening? In the case of Diversa this refers to library construction—once the DNA isolation is complete, what methods will maximize its incorporation into an environmental gene library that can be screened for product discovery purposes?
- Development of new technology: What should be included in terms of the costs associated with the development of new technologies, such as High Throughput Culturing by Diversa, that enable the discovery of novel products?
- Sample screening: Who will screen the samples for target characteristics? Which screens will be used?

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[5] Opportunity cost is the difference between the return on one investment and the return on an alternative.

- Protection of intellectual property: Once a suitable product is identified, how will the parties protect their work? Who bears the cost for patenting? Who bears the cost of exhaustive searches for possible patent infringements? Who bears the cost for defending the patent?
- Reporting costs: How will the costs be divided among the stakeholders associated with any regulatory reporting requirements?
- Product testing/regulatory compliance: Once the product has been developed, what tests or regulatory compliance checks must it undergo in order to make it legally marketable? Who bears those costs?
- Production: Once a product is market ready, how will it be produced in quantities suitable for sale? Who bears those costs?
- Marketing/distribution/sales: What are the costs of educating the market about the product and getting the product to customers, and who is responsible for those costs?

4.3 Benefit-sharing

Benefit-sharing is a key tenet of the CBD. For companies with a continuous need for new sources of genetic materials that can only be obtained through successful cooperation with countries possessing such genetic resources, a fair and equitable system of benefit-sharing is essential. Determining what is fair and equitable, however, is a matter of perspective and is tied closely to the valuation of the resource. In the distribution of benefits, collaborators should consider a wide range of benefit-sharing possibilities. Monetary benefits are only one type of benefit. There are many non-monetary benefits that collaborators can share that arguably contribute more to a country than the monetary benefits (Thayer 2003). Table 3 provides examples of both monetary and non-monetary benefits. These examples are the result of an analysis of a number of agreements on access to genetic resources (Tides Center/Biodiversity Action Network 1999). The range of the benefits presented below corresponds to the diversity of interests among stakeholders.

Table 3: Types of Benefits

Non-monetary	**Monetary**
Acknowledgements in publications	Bioprospecting fees (periodic, annual)
Joint research and increased scientific capacity	Per-sample fees
Participation in planning and decision-making	Percentage of royalties on net sales,
Control over samples and research results	Gross sales, licenses, etc.
Voucher specimens nationally deposited	Percentage of research budget
Co-ownership or sole ownership of IPRs	Commitment to re-supply in source country
Free access to technology and products resulting from agreements	Development of alternative income generating schemes
Protection of local existing applications of IPRs	Milestone payments
Technology transfer (equipment, material donation, sharing of know-how)	
Training in bioprospecting, collection and preparation of samples, biodiversity monitoring, socioeconomic monitoring, and/or nursery and agronomic techniques (increased conservation capacity)	
Political	
Advertising	
Educational	

Source: Based on Tides Center/Biodiversity Action Network (1999).

Given this discussion of property rights, it stands to reason that benefits should be shared equitably between the parties to the agreement, as well as the stakeholders. It also stands to reason that the amount of benefit each party requires bears some relationship to its level of contribution to the research and the final product or service.

Returning to CBD guidance, each nation that is Party to the Convention has sovereign rights over its own biological diversity. Therefore, how a country chooses to distribute the benefits will be determined by applicable laws and regulations and the stakeholders within the country. It is the value-added processing portion of the equation where both parties can make contributions. For instance, the more a provider country contributes to the research and development of a product, the more it can claim in terms of its fair share of the resulting benefits (profits, etc.). Furthermore, the provider country may also add value to the final product if it can contribute other inputs (e.g., production facilities or existing distribution chains) available for domestic or international sales. It may also be the case that, due to the costly technology or highly specialized skills required for research and production, some aspects of the value-added processing can only be performed by the biotechnology company.

The relative mix of contributions may evolve over time as well. For instance, when a biodiversity collaboration also includes some technology transfer, a company may train a country's scientists in a technique, such as sample collection, sample screening, or nucleic acid extraction. This would allow a country to provide a larger part of the value-added contribution as the biodiversity collaboration matures and more of its scientists are trained by the company.

5. Diversa Corporation and Biodiversity Collaborations

For biotechnology companies interested in developing biodiversity collaborations for the commercial use of genetic resources, crafting an approach that addresses each of the key issues discussed above is essential. This section describes the approach of Diversa Corporation, a publicly-traded American biotechnology company whose business involves the discovery and evolution of novel genes and genetic pathways from unique environmental sources. During a time when there existed few or no models, guidelines, or requirements, Diversa developed and refined a set of principles for selecting areas of the world in which to work, selecting partners with which to work, and for creating agreements with governments to help ensure long-term relationships based on the sustainable use of genetic resources.

5.1 Diversa and Its Technology

Diversa has patented technologies that allow it to rapidly and efficiently identify target substances from environmental samples to search for novel gene products in nature. Complimentary technology developed and used by Diversa enables portions of genes to be combined to provide the target characteristics as dictated by the target application and its market. Using its proprietary technologies in a process called directed evolution[6]. Diversa is able to evolve genes to create multiple variants based on the original nucleic acid. These genes are then screened for characteristics and activity required for the end product or application. The diagram below provides a simplified view of Diversa's business process. Biodiversity, the primary input to the process, is collected by Diversa's many biodiversity collaborators. This establishes the foundation of Diversa's Research and Development program. The resulting nucleic acid is captured into Diversa's proprietary environmental gene libraries, which are then screened for a host of various products. Once leads and hits are discovered, further enhancement and refinement can take place through Diversa's proprietary directed evolution techniques (see also figure 2). As evidenced

[6] Such proprietary technologies include Diversa's Gene Site Saturation Mutagenesis™ and Tunable Gene Reassembly.™

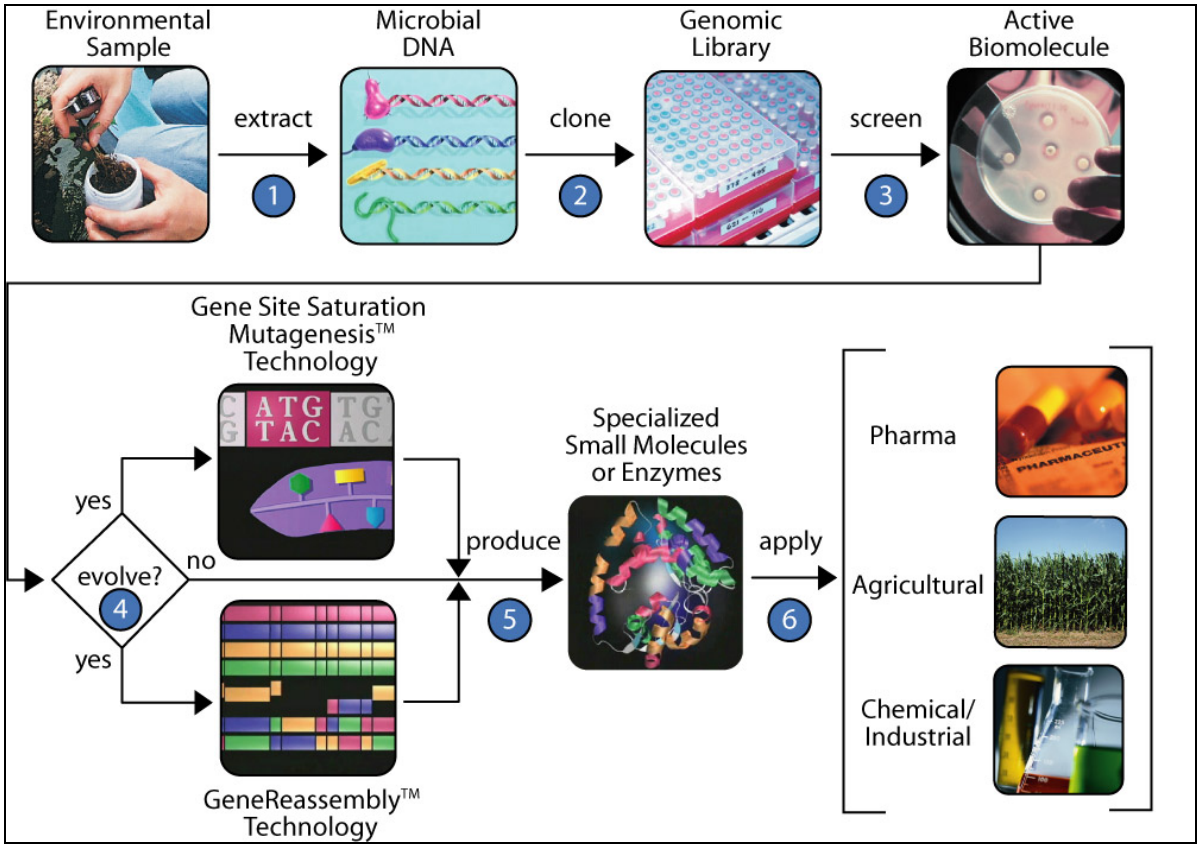
by Diversa's broad product portfolio, this process has effectively and efficiently developed applications and products at an unprecedented rate for a company of its size and age.[7] Diversa's unique proprietary approach to discover and evolve novel genes has created environmental libraries comprising millions of genomes.[8]

5.2 Diversa's Biodiversity Collaboration Approach: The Philosophy

Microbial biodiversity is the foundation for Diversa's Research and Development programs. It is through a principled approach that Diversa seeks to secure sustained, mutually beneficial access to these resources.

Diversa has entered into many agreements based on this criteria to enable access to unique biotopes in such places as Alaska, Antarctica, Australia, Bermuda, Costa Rica, Ghana, Hawaii, Iceland, Indonesia, Kenya, Mexico, Puerto Rico, Russia, the San Diego Zoo, South Africa, and Yellowstone National Park (see Figure 3 on next page). A critical component to this strategy is identifying good biodiversity collaborators who not only are sound in terms of their scientific capabilities, but also in a position to provide access to unique biotopes and habitats.

Figure 2: Innovation from Biodiversity and Gene Evolution



[7] Although it has had several names prior to 1997, Diversa traces its roots back to 1992 with two management co-founders, Eric Mathur and Jay M. Short. Today, Diversa has close to 400 employees. Through that period Diversa has produced hits, leads, products, and applications for pharmaceutical, agricultural, chemical, and industrial markets.

[8] As a point of reference, the human genome alone contains approximately 30,000 genes.

Figure 3: Unparalleled Biodiversity Access

Diversa follows CBD guidelines and supports and leads global corporate efforts to achieve the goals of the CBD through its biodiversity collaboration agreements.

Since recombinant DNA technology requires only one-time sample collection, Diversa's technology and sample collections have minimal impact on the environment. "If you hike in the park with a waffle sole shoe, you'll walk out with more soil than a bioprospector" (Marshall 2000). Furthermore, by reproducing and sustaining genetic diversity in their labs and collecting very small samples, Diversa's approach facilitates sustainability of both the resource and the source biotope/habitat. The importance of this point is that collaborations of this type will not negatively impact current or alternative uses of the biodiverse resource or environmental, social, or intergenerational issues.

In addition, through its exploration of biodiversity for commercially valuable genetic and biochemical resources, Diversa has facilitated the protection of wild lands and funding for conservation activities. Diversa believes that while these explorations should lead to new products, they should also bolster the economic and conservation goals of the provider countries while boosting the medical and agricultural advances needed to combat disease and sustain growing human populations.

Through its experience in facilitating and managing biodiversity collaborations over the past decade, Diversa has determined that there are three main factors that lead to a successful biodiversity collaboration and bioprospecting program:

- efficient and reasonable permit systems (requiring 3 months or less to secure a permit and oblige the permit holder to reasonable reporting criteria);
- efficient and reasonable benefit-sharing negotiations; and
- a goal of creating fair and trusting relationships that result in expanded, long-term cooperation.

5.3 Where to Start?

Although Diversa is located in San Diego, which is one of the world's 25 "Global Biodiversity Hotspots (see http://www.conservation.org/xp/CIWEB/strategies/hotspots/hotspots.xml), the genetic diversity that Diversa seeks occurs all over the globe. It selects areas for sample collection based on three basic criteria: 1) uniqueness of region, ecosystem, habitat in relation to the sources of Diversa's previously acquired samples; 2) the similarity of the environmental conditions with those conditions required by the final application and product; and 3) whether or not the area is located within one of the 25 Global Biodiversity Hotspots. Diversa has entered into many agreements to enable access to unique biotopes based on these criteria. A critical component to this strategy involves identifying biodiversity collaborators that are both sound in terms of their scientific capabilities and in a position to provide access to these unique biotopes.

The selection of a partner country is a complex process. There are a number of factors important to the creation of a biodiversity collaboration. Diversa has criteria for partner selection and requirements that must be met in order for it to engage in bioprospecting.

5.3.1 Collaboration Criteria for Partner Countries

The first step Diversa takes when exploring options for new biodiversity collaboration is to assess countries according to the following criteria:

- ***Legal framework and political will*:** Unfortunately, many countries have not yet fully addressed the legislative and regulatory issues required to establish and foster bioprospecting activities and biodiversity collaborations. Yet, in some countries where significant legislation on biodiversity exists, it may be so comprehensive and complicated that it becomes too cumbersome to foster bioprospecting. For example, in the Philippines, many government agencies are required to review and approve bioprospecting projects in order to secure governmental consent. As a result, very few proposals have been approved, and even more have likely never been submitted because of the low likelihood of success. In other cases, problems may lie with IPR protection. Often procedures for exporting DNA samples do not exist. Typically government agencies that become involved with overseeing and processing the forms and documents required for such activities, such as customs and public health officials, are seeing them for the first time. In these cases, political will on the part of the government to help orient and train their officials on matters pertaining to bioprospecting activities is critical to the success of any international bioprospecting initiative.
- ***Equal treatment for all companies*:** It stands to reason that a country should view all potential commercial collaborators equally, such that all companies collecting samples should be required to enter into government sanctioned bioprospecting agreements that follow the guidelines and support the objectives of the CBD. This can demonstrate to potential partners that the country has standardized its approach to biodiversity collaborations and that access agreements based on internationally-accepted principles are in place. It thus ensures the sustainable use of biodiversity and supports the fair and equitable sharing of benefits derived through the biodiversity collaboration. This policy and framework also requires an understanding of the differentiated risks associated with different collecting techniques and approaches.
- ***Strong scientific and conservation partners*:** Appropriate scientific capabilities, such as skills, equipment, and infrastructure among collaboration partners, speeds the process of narrowing the search for target organisms. As these partners receive training, they are able to provide more value-added services.
- ***Unique and protected habitats*:** A greater diversity of habitats translates into a greater diversity of environmental libraries for Diversa, and consequently increases the chances of discovering a novel and unique gene for a new product or application. Diversa also prefers to collect samples from protected habitats so as to maintain the consistency and long-term viability of the genetic resource.

5.3.2 Diversa's Bioprospecting Framework

After identifying the country of interest and the institutional candidate, Diversa employs a bioprospecting framework it has developed over the past decade to help guide the structuring of the collaboration agreement. This framework has evolved significantly both through Diversa's own implementation of biodiversity collaborations and through monitoring and adapting to changes within international conventions, such as the CBD. The main tenets of this framework are:

- ***Legal rights to genetic resources*:** Using the CBD as a guide, Diversa recognizes that governments are the stewards of biodiversity in each country and that they alone hold the authority to grant access. Therefore, Diversa prefers to work in countries that are able to assign and clearly define Diversa's legal rights with regards to the use of environmental samples and associated genetic material.
- ***Prior informed consent*:** Recognizing that land owners and managers have a stake in the bioprospecting activities, Diversa requires its biodiversity collaborators to secure informed consent from land owners and managers prior to collecting samples.
- ***Rights to patent and commercialize*:** Diversa must maintain the *right* to patent and commercialize genes and gene products derived from samples. The patent is the basis for protection of any intellectual property developed during the collaboration agreement. The right to commercialize is critical to facilitating the creation of benefits that can be shared by the biodiversity collaborators, and the distribution of benefits will be determined by the parties in the biodiversity access agreement. As mentioned previously, those terms are determined based on the intellectual contribution and on the overall contribution to the research and commercialization effort required to produce the end product.
- ***No competition between the biodiversity collaborators.*** Diversa has proprietary technologies that enable the processing of the enormous amounts of genomic information required to identify new gene products from environmental samples. Diversa does not want the proprietary technology it transfers to its biodiversity collaborators to be used in any way by that institute to compete against Diversa. Accordingly, strict and conservative interpretations of confidentiality are critical ingredients towards developing a productive relationship.
- ***No transfers to third parties*:** Since Diversa's greatest competitive advantage within the biotechnology industry is its proprietary technology, it is critical that it not be shared with third parties that could compete against Diversa. This technology transfer is for the benefit of the collaborator in the context of its own capacity building. According to their commitment to fairness, Diversa also respects and protects the confidentiality of its biodiversity collaborators' proprietary technologies.
- ***No exclusivity requirements*:** Diversa encourages its biodiversity collaborators to enter into similar bioprospecting projects with other life science research companies. The more biodiversity collaboration agreements, the more viable the biodiversity collaborator and the more resources they have to preserve biodiversity in their country.

5.3.3 Benefit-sharing Mechanisms

The next step in developing the collaboration is to create a benefit-sharing agreement that encourages the sustainable use of the genetic resource. Diversa has developed a complete set of benefit-sharing mechanisms, both monetary and non-monetary. These mechanisms allow Diversa to provide incentives for biodiversity collaboration while working within international guidance and remaining responsible to its shareholders.

5.3.4 Non-monetary Benefit-sharing

Diversa uses many of the non-monetary benefits listed in Box 3 in its biodiversity collaboration program. Diversa and its biodiversity collaborators have a broad spectrum of benefit-sharing mechanisms from which to choose to meet the specific requirements of the collaboration and associated stakeholders. The non-monetary benefits it can offer build capacity and are particularly important to both the company and the collaborator. These benefits will allow the collaboration partner to do more of the value-added work in country.

- ***Technology and training*:** Diversa has enhanced scientific capacity among its biodiversity collaborators through the transfer of technology and training. Using its proprietary screening technology, it can assist countries to catalogue their microbial diversity. This allows the country to better understand and manage their ecosystems and resources. Diversa can also train collaborators in DNA isolation, a key step in cataloguing molecular diversity as well as in creating the environmental libraries that Diversa will screen for target compounds. Additional training in various molecular techniques further enhances the scientific capacity of the collaboration partner.
- ***Supplies and equipment*:** The in-kind contributions of supplies and equipment from Diversa to its biodiversity collaborators make the biodiversity collaboration more efficient. In some cases, Diversa has supplied sampling equipment and lab supplies. In cases where partners are constrained by lab resources, providing lab equipment has enabled an expansion of research activities on the part of its biodiversity collaborators.
- ***Research support*:** Diversa has also worked with biodiversity collaborators to provide special research support, such as helping them conduct microbial taxonomic studies and biodiversity inventories. For example, Diversa conducted genetic analysis of the Yellowstone wolves that provided the Park with a full pedigree of their wolves. Diversa also helped Yellowstone with a microbial assessment of a black smoker spire that came from the bottom of Yellowstone Lake.

5.3.5 Monetary Benefit-sharing

Listed below are monetary benefit-sharing mechanisms that Diversa has used in its biodiversity collaboration agreements.

- annual payments
- sample collection costs
- per sample payments
- milestone payments (associated with performance of biodiversity collaborators), and
- royalties.

While these benefits do not need explanation, several observations can be made about the negotiation process. It is clear to Diversa that biodiversity collaborators who are more flexible about the mechanisms of monetary benefits will be more favorably positioned to capture the most value, primarily because there is so much unknown about potential discoveries. In some cases, once the market for a prospective product is well understood, it will be easy to determine the revenue potential of a product. For markets with relatively small potential payouts, however, collaboration partners may favor receiving sure payments for performance up-front versus some portion of unknown future royalties. Conversely, when there are many potential applications coupled with potentially large revenues, biodiversity collaborators may be interested in a larger share of royalties at the expense of up-front payments, hoping for a percentage of a larger payout.

It is likely, however, that the market potential at the outset of the collaboration will not be obvious. In these cases, graduated royalties could be used, which changes the percentage of proceeds from the product sales according to variables such as the sales volume or end-product market segment.

Some factors to consider when discussing monetary benefits include:

- potential market for a target product;
- current need for money;
- required investment to bring a product to market; and
- probability of successful product as a result of collaboration.

5.3.6 Results

As a result of Diversa's biodiversity collaborations, it has established a global network of partners that provides access to a wide array of diverse ecosystems and habitats. This diversity has created vast environmental libraries, products, and a robust product pipeline. Diversa secures rights to discoveries resulting from this cooperation and fosters an image that facilitates other biodiversity collaborations.

Diversa's collaboration partners have received more than USD 2 million in financial payments and USD 2 million in third-party grants to support their work with Diversa. In addition, Diversa has trained more than 100 scientists worldwide, provided improvements to infrastructure and scientific capacity, and has even helped individual scientists further their college and post-graduate studies.

5.4 Case Study: Diversa Corporation and the Russian Federation

5.4.1 The Project

In 1994, the United States Department of Energy (USDOE) began a program called *Initiatives for Proliferation Prevention* (IPP) that provides seed capital, matched by corporate funds, to scientists formerly engaged in the Soviet Union's weapons program. The goal is to create saleable products in commercial ventures (Chase 2001). The program provided a vehicle to productively re-engage the highly-skilled scientists that remained in the constituent republics after the fall of the Soviet Union in 1991. In 2004, the program had 153 projects underway at 56 institutes in Russia[9]. Each project is managed by one of USDOE's national laboratories. Diversa's first IPP project in Russia was administrated by the Idaho National Engineering and Environmental Laboratory (INEEL).[10]

In 2000, the Center for Ecological Research and Bioresources Development (Center) was created with the assistance of USDOE and the World Foundation for Environment and Development (WFED) to manage the biodiversity collaboration under this program. The Center was one of the first institutions in Russia to obtain NGO status. It was also the first organization to secure legal rights to ship biological samples out of Russia.[11] The Center's functions include:

- ensuring conservation and sustainable use of Russian biological diversity;
- coordinating negotiations/contracts for access to Russian biodiversity, ensuring benefit-sharing agreements that generate economic and scientific benefits for the participating Russian partners;
- acting as an information clearinghouse;
- providing project-directed financial support; and
- coordinating joint research activities.

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[9] From Initiatives for Proliferation Prevention website: www.lanl.gov

[10] www.inel.gov/

[11] Science Beat, Lawrence Berkeley Laboratory, July 28, 2003; www.lbl.gov/Science-Articles/Archive/LSD-return-to-Kamchatka.html and CERBRD www.bioresources.ru/

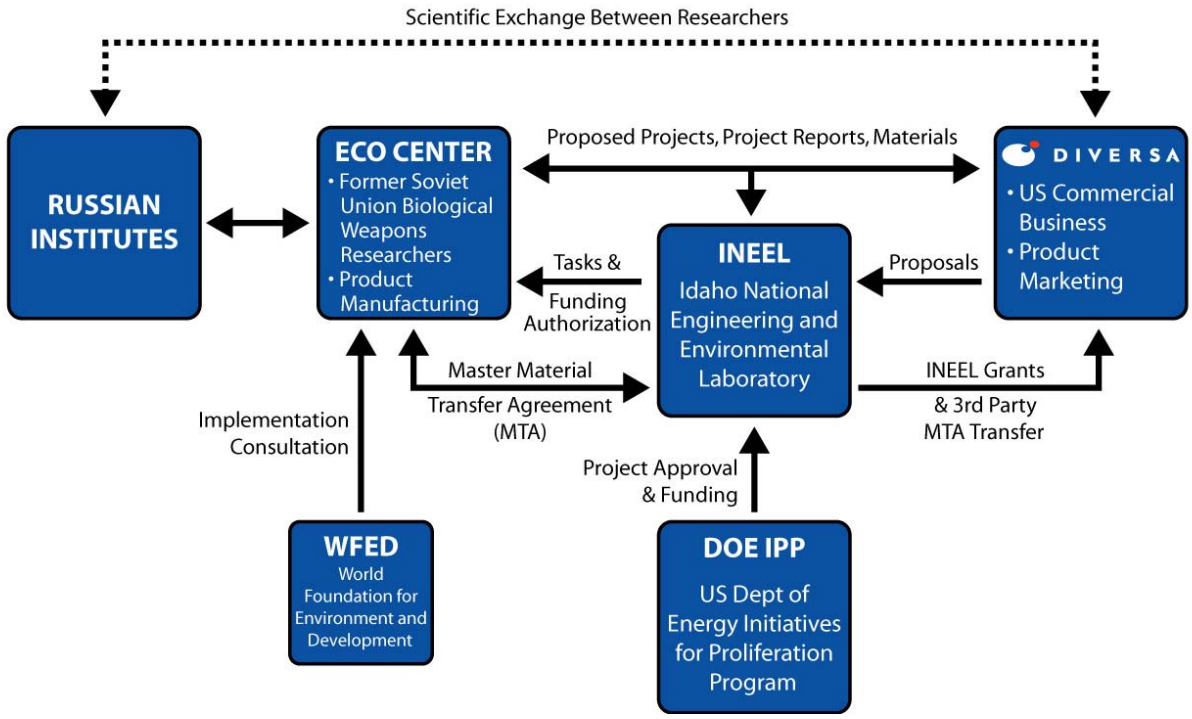
As a hub for administrative streamlining, it was the Center, with the support of the Russian Government, that blazed the first trail to legally export biological materials from Russia to Diversa since Russian President Vladimir Putin's election. Previously, Russia lacked appropriate mechanisms to characterize and document the biological materials produced by its scientists through this biodiversity collaboration. The Center and the Russian Government created the appropriate capacity for its regulatory bodies to evaluate the safety of biological materials for export.

Starting in November 2000, Diversa partnered with four Russian Institutes through this program: the Institute of Biochemistry and Physiology of Microorganisms (IBPM), the All Russian Research Institute of Phytopathology (ARRIP), the Research Center for Toxicology and Hygienic Regulation of Biopreparations (RCT&HRB), and the State Research Center for Applied Microbiology (SRCAM).

Under a Cooperative Research and Development Agreement (CRADA) between Diversa and INEEL, IPP provides the Russian Institutes with annual payments of approximately USD 350,000 to implement projects selected by Diversa. INEEL received USD 150,000 to administer the program for the US Government. Diversa receives no direct funding, but contributes to the collaboration with some matching funds and capacity development. Over half of the scientists Diversa has trained in its biodiversity collaborations are from Russia.

As illustrated in the Figure 4, the mechanism of interaction is complex. Most importantly, on substantive scientific issues there is direct communication between Diversa and the institutes. From Diversa's perspective, the process starts with a proposal for a project from Diversa submitted to INEEL. This proposal is jointly developed between Diversa and the institute or institutes in Russia that will work on the project. If approved, INEEL funds it and the institutes conduct the work in close communication with Diversa. The Center oversees the financial transactions, scientific reporting system, and the transfer of supplies, equipment, and, of course, biological materials to and from the US. This work is transferred

Figure 4: Model of Interaction between Biodiversity Collaborators in Russia



Source: Management diagram developed by Rob Rogers from INEEL.

via the Center to INEEL on the basis of a Master Material Transfer Agreement (MTA). The samples are then conveyed to Diversa via a third party MTA between Diversa and INEEL. WFED played a role in the establishment of CERBRD.

5.4.2 Experiences to-date

In this biodiversity collaboration, the Russian Federation provided access to its biodiversity. Its scientists not only helped Diversa select the appropriate biotopes for targeted sampling but also provided significant value-added processing in isolating and characterizing the strains.

During the four years of Diversa's cooperation with the Russian Federation, both sides encountered numerous challenges. These challenges ranged from those typical in new business relationships, such as developing a working relationship, to those which were unique to this collaboration, including:

- bureaucratic delays both in the US and Russia related to national security issues;
- introduction of new legislation governing the transfer of biological materials;
- development of customs regimes for shipping supplies and equipment;
- quality of equipment available to the partners; and
- property rights for samples.

While cooperation on these issues has been successful, some of these issues remain challenges for ongoing project activities. It is important to note, however, that the experience of facing the challenges together has strengthened the relationship between Diversa and its Russian partners, which, in turn, has improved the efficiency of the collaboration.

5.4.3 Benefits to Diversa

Despite the complexities presented above, the collaboration has worked well for four years. Certainly, the political will of the Russian government and continued funding from the American government have fostered patience on both sides to continue building the collaboration and exploring commercial research opportunities. In fact, the funding provided by DOE's IPP program enabled Diversa to launch this biodiversity collaboration. Without it Diversa may have never initiated a biodiversity collaboration in Russia. In addition, the trust developed between the research collaborators and the successful completion of joint work has been critical for the project to reach its stated objectives. Table 4 shows the benefits to Diversa resulting from cooperation over the past 4 years.

Table 4: Russia Samples sent to Diversa

Total Samples Received from Russia:	1838
- Environmental	373
- Isolates:	1465
By Year:	
- 2000	34
- 2001	165
- 2002	185
- 2003	1454
Total Environmental Gene Libraries:	89

Note: Diversa averages roughly 2,500 samples per year. Each environmental sample consists of about 200 grams of soil or other sample type. Diversa also has over 3,000 gene libraries.

Beyond the physical benefits of the environmental samples, nucleic acid, and microbial strains that Diversa received, it has also benefited from:

- trust gained on both sides, which has improved the overall quality of collaboration;
- a legal path towards enabling the export of biological materials from Russia to Diversa through the combined efforts of the Center and the Russian Government;
- access to one sixth of the Earth's land surface area;
- access to one of Earth's 25 Global Hotspots (the Caucasus located between the Black and Caspian Seas just North of Georgia); and
- solid relations with the Government of the Russian Federation.

5.4.4 Benefits to the Russian Partners

Under the IPP project, Russian scientists in the four institutes and in the Center receive direct payments for their work. In many cases, they receive this amount in addition to their state wages. Supplementing these monetary benefits, the Russian scientists also received substantial non-monetary benefits including:[12]

- laboratory and office equipment and supplies;
- training in Diversa techniques by Diversa scientists (to date, Diversa has trained over 50 Russian scientists);
- access to new modern equipment for conducting research;
- reorientation to long-term, commercial projects (In addition to building capacity through training in molecular techniques, the scientists and institute leadership have gained knowledge that has enhanced their ability to operate sustainably on non-military projects in the future.);
- opportunity to apply unique molecular techniques to Russia's vast biological resources, and to foster sustainable use of Russia's genetic resources; and
- development of new products and technologies, as well as the possibility of receiving royalties from products and technologies that are developed by or through Diversa.

As a result of the successful partnership forged through this biodiversity collaboration over the past four years, USDOE has provided an additional year of funding to maintain the project in recognition of the progress achieved to date and the significant challenges that were faced by all participants during the first years of the collaboration. Currently, Diversa is evaluating opportunities to expand its business in Russia through both its existing products and those that have become viable through its collaboration with the Russian institutes. Diversa's interaction with its Russian partners illustrates how non-monetary benefits from biodiversity collaboration have enhanced institutional capacity, fostering an environment in which all participants are eager to continue expanding the collaboration.

6. Conclusions

Internationally-accepted principles of conduct concerning the commercial use of biodiversity provide direction for biodiversity collaborations between public and private entities. Using the CBD and TRIPS as a guide, the two most important issues to address in undertaking biodiversity collaboration are property rights (intellectual and others) and the appropriate valuation of biodiversity.

[12] Contributed by Dr. Alexander Denisov of RCT&HRB, one of Diversa's collaborators.

As a general proposition, the market value of any biodiversity-derived product is the natural limit to the monetary value of biodiversity, and this also sets the limits to the contributions required to convert it into revenue-generating products. This underscores the necessity for companies, governments, and other stakeholders to realistically and fairly value their contributions to the production process. Participants should also recognize the importance and inherent value of a wide range of non-monetary benefits. In addition, the parties to the biodiversity collaboration must consider the contribution of other stakeholders and their possible entitlement to some portion of benefits resulting from sales of a product generated through biodiversity collaboration.

The example of Diversa draws into sharp focus the main issues challenging biodiversity collaborations between the private sector and governments. While the CBD and other international agreements provide general guidance on biodiversity collaborations, Diversa has adopted a set of principles based on these agreements that guides its biodiversity collaborations and provides many examples of how to implement such initiatives. Through its many biodiversity collaborations, Diversa has developed a successful and replicable model for properly and effectively implementing bioprospecting activities in various legal and political frameworks around the world. While the CBD continues to mature, and as the Parties improve their ability to attract biotechnology companies and oversee bioprospecting activities in their respective countries, Diversa has shown that it is dedicated to supporting those efforts and maintaining itself as the global leader in bioprospecting.

Through Diversa's biodiversity collaborations, it is also evident that the establishment of property rights, commercialization rights, and the appropriate valuation of genetic resources are critical to initiating bioprospecting activities and maintaining their long term viability and success. On the basis of both monetary and non-monetary benefits, it is clear that a relatively small- to medium-sized biotechnology company, such as Diversa, can successfully establish and implement bioprospecting activities through such biodiversity collaborations. These biodiversity collaborations illustrate that there are many ways a biotechnology company can sustainably use biodiversity and incorporate measures to protect resources, habitats, and the environment.

Finally, the case study on the partnership between Diversa and the Russian Federation supports the assertion that successful biodiversity collaborations result from principled approaches. These collaborations evolve, not only with training and technology transfer, but also as the result of the working relationships that they foster over time.

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Implementing the Principles of the United Nations Convention on Biological Diversity:

The Experience of Kina Biotech in Peru [1]

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Origins

The biotechnology start up company Kina Biotech S.L. was conceived with Iberomerica in mind. Initiating operations in Spain, the founding team established contacts and negotiated commercial contracts with the aim of commercially valorizing biological diversity in Peru and Colombia. It's history goes back to *Instituto de Empresa*, one of Europe's leading business schools. Located in Madrid, Spain[2], the company's founders met there while studying for their International Executive MBA degrees. Set up in September 2002, the company received its initial economic support from the Regional Council of the Historical Territory of Bizkaia (Diputación Foral de Bizkaia[3]) under the framework of the Sustatu Bideberri Programme. In September 2003 the company established Kina Biotech SRL, an affiliate in Peru.

Mission

The term *Kina* refers to the Quechua name for the "quina" tree, also known as *Cinchona officinalis*. The name was proposed by Linnaeus in honour of the Countess of Chinchon, who in the 17th century was successfully treated for malaria with an infusion of extracts from its tree bark. One of the first documented contributions from the New World to the Old World's pharmacopoeia, the active ingredient was later given the name quinine.[4]

Inspired by this example of history, Kina Biotech seeks to systematically pursue the potential of the region's biodiversity, improving the quality of life and health for people everywhere by valorising the plant and microbial biodiversity of the Andean region.

The countries comprising the Andean Community of Nations[5] (Bolivia, Colombia, Ecuador, Peru, and Venezuela) possess a considerable proportion (over one third) of the world's plant biodiversity. Some of these countries still conserve large tracts of unspoiled natural ecosystems, a potentially valuable source of raw materials with new pharmacological ingredients.

Activities of the Company and Founding Team

Our activities include commercial valorization of natural resources from Andean countries for their use in the pharmaceutical, cosmetic, and nutraceutical industry. A key link in this value chain, we efficiently procure legal access to resources for our industrial clients and provide effective, unique research tools with high added-value services for discovering active ingredients.

Our research tools are based on chemical and genetic libraries generated from plant and microbial material. Extracts are processed using innovative techniques in the field of analytical chemistry and biotechnology performed at our laboratories in Bilbao (Bizkaia), at the Bizkaia Technology Park[6] that is also home to our corporate headquarters.

Kina Biotech also has an innovative business approach. Our competitive advantage derives from our multi-national Iberomerican dimension and strong commitment to social responsibility in the mega-diverse countries of the Andean region, whose biodiversity wealth can only be developed through environmentally safe practices.

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2 http://www.ie.edu
3 http://www.bizkaia.net/Ekonomi_Sustapena/home/in_index.asp
4 http://www.rain-tree.com/quinine.htm
5 http://www.comunidadandina.org/endex.htm
6 http://www.parque-tecnologico.net/english/english.htm

The founding team brings together diverse nationalities and backgrounds. Their complementary areas of experience includes the creation of technology-based companies, financial management, business development and strategic alliances, international legal consulting for World Bank projects, public and private sector research management, and corporative development in biotechnology multinationals. Their capabilities are the foundations of our business success.

Target Markets

Kina Biotech's target markets are the pharmaceutical, cosmetic, and nutraceutical sectors, and we put our products and services at the disposal of the R&D departments of clients doing business in these sectors.

The world pharmaceutical market is worth $300 billion in annual sales. Highly competitive (the big pharmaceutical companies control 80% of it), this market's optimal annual growth rate is 10%, which for a major company means introducing two or three new pharmaceutical products every year. The pharmaceutical industry today, however, is suffering from a scarcity of new products. There is little in the pipeline or product portfolio to replace products that can no longer compete in the marketplace or whose patents are expiring. The search for economic profitability has grown even stronger due to restrictive government health spending policies and the increasing prevalence of generic drugs.

The cosmetic industry's annual global turnover is estimated at $170 billion. The main consumer markets are the European Union, Japan, and the United States. With per capita consumption rates of over $100, there is a bright future for strong growth.

The nutraceutical, or functional food industry, is a $50 billion market and it has the greatest growth potential for Kina Biotech.

Bioprospecting

Bioprospecting is the systematic search for genes, compounds, designs, and organisms that may have potential economic use. Natural products have always been a traditional source of new active compounds, but now pharmaceuticals are also derived from new combinatorial chemistry, complemented in some cases with microbial biodiversity research (an activity that accounts for 25% of discovery work). Plant bioprospecting still accounts for at least 10% of the discovery work of big pharmaceutical companies.

Although they explore different sources of biodiversity and use tools of varying degrees of technological sophistication, bioprospecting companies operating at the early stages of the value chain share a number of common features. They act as intermediaries between the suppliers of plant material, sovereign countries, and industry, enabling active compounds to be identified for specific therapeutic areas. The most common bioprospecting models are defined in relation to:

- Public or private institutions (in terms of their management and/or funding).
- Companies carrying out field work with their own resources or via sub-contractors (including academic collaborators).
- Intermediary companies in the value chain or companies participating in the process from discovery to the marketing of drugs.

Products and Services Offered

Kina Biotech provides services for pharmaceutical, cosmetic, and functional food sectors that require the preparation of laboratory samples for subsequent delivery to clients. In the short term, the company generates income by providing these services. Over the long term, it will offer new services with greater added value and also develop its own products. The company therefore will conduct its own research. Kina Biotech offers three classes of chemical products:

1. Crude extracts of natural products originating from plants representative of the Andean countries. This supply of crude extracts catalogued according to their taxonomic classification and geographical origin (making it possible to return to the source) represents the first level of tools available to industrial clients.
2. Chemical libraries derived from the fractionation and cataloguing of compounds found in the extracts obtained by Kina Biotech. This is a tool of greater added value for industrial clients. These libraries can be used in conjunction with specific therapeutic trials to identify possible bioactive compounds.
3. Purified compounds that are potential active principles. This is the company's greatest added value product. Kina Biotech's use of pharmaceutical-genomic tools allows for molecular-based screening (based on known disease marker genes) that can identify therapeutically active chemical compounds for use in pre-clinical and clinical trials by clients in the pharmaceutical industry, thereby greatly speeding up their search process.

Kina Biotech, S.L. also offers genetic libraries of plant and microbial origin as molecular products. All of the products referred to above come with customer service that provides access—by means of a security code—to a personalised database that can combine relevant information on the geographical and biological origin of compounds with information about their structure and function.

Applying the UN Convention on Biological Diversity in Peru

In line with the company's ethical guidelines, access to natural resources, plants, and micro-organisms, as well as the raw material processed by Kina Biotech, is subject to a legal contract with the competent authority in the mega-diverse country concerned, in accordance with the recommendations of the United Nations Convention on Biological Diversity and the rules of the supra-national legal system of the Andean Community of Nations.

The United Nations Convention on Biological Diversity recommends the establishment of a national legal framework that envisages, among other things:

- Setting up rules for access to biological and genetic resources;
- Protection of indigenous and local knowledge of natural resources;
- Enactment of national laws for the protection of indigenous and local knowledge based on the use of natural resources;
- Promotion of biological innovations that make use of resources;
- Enactment of specific laws on the intellectual property of breeders of plant varieties;
- Establishment of intellectual property laws giving rights to the inventors of technological innovations.

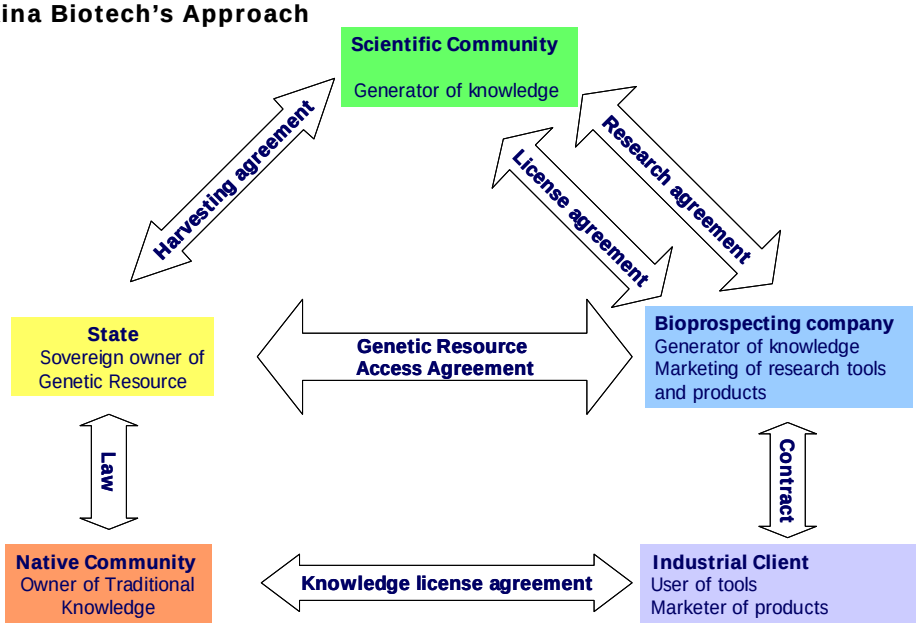
At the supra-national level, the Andean Community of Nations has transposed the recommendations of the United Nations Convention on Biodiversity into the following decisions under regional law, also known as the Acuerdo de Cartagena:[7]

- Decision 345 of October 1993 defines the common provisions on the protection of the rights of breeders of new plant varieties;
- Decision 351 of December of 1993 establishes a common regime for copyright and related rights;
- More specifically linked to genetic resources is decision 391 of July 1996, which sets out common provisions on access to genetic resources for commercial valorization purposes. This decision also makes reference to the intangible element—traditional knowledge—associated with the use of resources, although regulation of such knowledge is left to a future directive;
- Decision 486 of December 2000 defines common provisions on intellectual property. Patent rights come under this decision.

Kina Biotech implements the following steps to equitably distribute profits from the commercial valorisation of natural resources (see also figure 1 for a schematic representation of the different material flows and other elements):

First, it sets up a research agreement with the national scientific institution it is collaborating with and also obtains a licence agreement to use the knowledge generated by the scientific community, which, contrary to research clauses with large multinational companies, retains intellectual property (including patent rights). One example of this type of agreement was established with a consortium, once funded by the ICBG program, led by Washington University in St. Louis[8] (MO, USA), where academic collabora tors from Peru included Universidad Peruana Cayetano Heredia[9] and Universidad Nacional Mayor de San Marcos[10]. The Confederación de Nacionalidades Amazónicas del Perú (CONAP),[11] representative of four

Figure 1: Kina Biotech's Approach



[7] Documents cited can be retrieved from: http://www.wipo.int/documents/en/meetings/2001/igc/pdf/grtkfic1_11.pdf (in English; Spanish is also available)
[8] http://www.wustl.edu
[9] http://www.upch.edu.pe
[10] http://www.unmsm.edu.pe
[11] http://wbln0018.worldbank.org/ESSD/indigenous.nsf/0/9ad43baf1f5164df852567fd005c5815?OpenDocument

federations of the Aguaruna tribe, also belongs to the consortium. The license agreement establishes rights to the consortium resulting from down and milestone payments as well royalties from futures revenues generated by Kina Biotech.

Secondly, the company applies for the state's consent to collect samples in collaboration with a national scientific institution. A contract is signed directly with the state for access to genetic resources and to allow for the marketing of tools and products derived from the study of biodiversity. In Peru, the governmental agency in charge is the Instututo Nacional de Recursos Naturales, which is part of the Ministry of Agriculture. These contract agreements are based upon the directives of Decision 391 of the Acuerdo de Cartagena. Depending on therapeutical areas of interest and specific processing requirements, research tools are placed under a commercial contract with clients in the pharmaceutical, cosmetic, or nutraceutical sectors. The company also offers to conduct high throughput cyto-toxicological studies as a pre-screening service to customers.

Significantly, our system does not lose sight of the important contributions made by the intangible component of intellectual property. In the case of Peru, the state recognises the right of native communities to preserve and attach value to their traditional knowledge. The final client accordingly enters into a knowledge licence agreement directly with the native community so that they can use such knowledge. This is the case for the Aguaruna federations belonging to the above-mentioned consortium. They benefit economically both from a knowledge licence agreement and from down and milestone payments, as well as from royalties subscribed in the license agreement signed with Kina Biotech. The mechanism proposed by Kina Biotech envisages:

- Contractual recognition of the ownership of genetic resource by sovereign countries and of intellectual property by indigenous communities and the local scientific community;
- Identification of the role of each party and recognition of the need for active participation by all parties involved in the value chain;
- Contractual commercial mechanisms that guarantee the equitable distribution of profits generated by resource valorization in proportion to their added value contribution;
- Development of technical and management skills to assure the sustainable development of the country originating the resource.

The key to success lies in all participating parties making their specific contribution:

- The sovereign state which owns its resources and regulates their use;
- The scientific community, which generates knowledge, holds intellectual property rights (patents), and contributes to technological development;
- The native communities which hold the intangible component (traditional knowledge) and the intellectual property rights to it; and finally
- the companies that make investments, develop products, and attach value in the marketplace.

Another important key to success is the fostering of international cooperation. In the case of Kina Biotech we have established projects with CYTED Iberoeka programme[12] and the Convenio Andrés Bello[13].

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[12] http://www.cyted.org/menu5/ProyectosIberoeka.asp

[13] http://www.cab.int.co/

Bioprospecting Partnerships in Practice:

A Decade of Experiences at INBio in Costa Rica [1]

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[1] Cabrera Medaglia J. 2004. Bioprospecting Partnerships in Practice: A Decade of Experiences at INBio in Costa Rica. *IP Strategy Today* No. 11-2004. Pp. 27-40.

[2] The opinions expressed in this paper are the personal opinions of the author and do not necessarily represent those of INBio.

Executive Summary

The National Biodiversity Institute (INBio) was created in 1989 as a non-governmental, non-profit association for private founding members. Its mission is to promote a new awareness of the value of biodiversity, and thereby achieve its conservation and use for the improving the quality of life.

Utilizing biodiversity can create new economic value and promote conservation, but it also presents both opportunities and challenges for managing infrastructure investments and human resources. In 1991, INBio developed the concept and practice of "bioprospecting" as one answer to the need to sustainably use Costa Rica's biodiversity for society's benefit. Continuing to gain acceptance in government, scientific, academic, and managerial circles, this concept refers to the systematic search for new sources of chemical compounds, genes, proteins, microorganisms, and other products that possess current or potential economic value. These constitute our natural biological wealth.

INBio has a formal agreement with the Ministry of the Environment & Energy (MEE) that allows it to explore the use of biodiversity and promote its national inventory in government-protected areas. Under this agreement, INBio actively develops biodiversity prospecting in protected wild areas of the country, in participation with national and international academic and private sectors. Research is carried out in collaboration with investigation centers, universities, and national and international private companies through investigation agreements. These include such key elements as:

- Access: limited in time and quantityEquity and compensation: esearch budget, benefit sharing (royalties, milestones, etc.)Technology TransferTraining in non-destructive activities
- Up front payment for conservation.

The agreements specify that 10% of the research budgets and 50% of future royalties will be donated to the Ministry of the Environment and Energy (MEE) and reinvested in conservation. The research budget supports the country's scientific infrastructure, and activities of added value aimed at conservation and the sustainable use of biodiversity. To-date, no royalties have been paid and no product has reached the market, but some products are under development, especially in ornamental and herbal areas.

1. Introduction

The importance of biotechnology for food, agriculture, human health, environmental protection, etc., has been outlined by diverse studies and emphasized by entities such as the Food and Agriculture Organization of the United Nations and the United Nations Environment Programme. At the same time, accessing and acquiring these technologies is especially complex due to their proprietary character (patents, plant breeder's rights, and other intellectual property rights). In the great majority of cases, big transnational firms own these rights. This is because they have the financial capacity to allocate R & D resources for new products and biotechnological processes.[3]

In order to close the gap between those who control these technologies and those who need them, many different schemes have tried to facilitate the access and transfer of biotechnology, mostly in agriculture. One of the most well known is the programme of the International Service for the Acquisition of Agri-biotechnologies (ISAAA).[4] Another interesting attempt has been tried in Costa Rica by the National Biodiversity Institute (INBio). Through agreements on access and the supply of biodiversity (samples and extracts), important technology has been acquired (not always involving biotechnology) that has

[3] In many occasions conflicts have even arisen because of patents granted to different firms that overlap or because the utilization of a product or process leads to confrontation with different patent holders (e.g., technology used, promoters, etc.)

[4] See Krattiger (2000).

helped to consolidate a basic infrastructure that can add value to resources and facilitates the discovery of new intelligent uses for genetic resources. As both a private institution of public interest and a non-profit charter, INBio can share important experiences about how to spread benefits derived from access to genetic resources. Of particular interest is the 1991 Merck and C. Agreement.

INBio's experience illustrates how the objectives of the Convention on Biological Diversity can be achieved by sharing the benefits derived from access to genetic resources, including the transfer of technology. It also reveals the importance of the collaborative agreements that allow our countries to access the technology and know-how needed to add value to biodiversity. Such agreements contribute to the conservation and sustainable use of our biodiversity and thereby improve our quality of life.

2. INBio's Experience

This section presents a brief summary of the most important, successful and promising agreements by INBio. The information is based on data provided by INBio's Bioprospecting Unit.

2.1 Research Collaboration Agreements with Industry

INBio-Merck: Search for sustainable uses of Costa Rican biodiversity

This was the first agreement signed with a commercial company (October of 1991). It allowed Merck to search for sustainable uses of Costa Rican biodiversity of interest to the pharmaceutical industry and veterinary science. It was renewed in 1994, 1996, and 1998 in similar terms. Studies to determine the potential use of a limited number of extracts of plants, insects, and environmental samples have been completed, and the agreement has given INBio access to technology, teams, and training.

Chemical prospecting in a Costa Rican Conservation Area

This project began in 1993 and ended in September 1999. Financed by the United States' National Institutes of Health (NIH), it was one of the world's five International Groups of Cooperation in Biodiversity (ICBG). Located in the Guanacaste Conservation Area, collaborators included the University of Costa Rica, Cornell University, and Bristol Myers Squibb. It examined tropical insects for possible pharmaceutical products and increased the local human resource capacity in ecology, taxonomy, and ecochemistry.

INBio-Givaudan Roure: Fragrances and Aromas

Constantly searching for new ways to utilize our biodiversity, in 1995 INBio began to explore its potential for fragrances and aromas with the company Givaudan-Roure. Aromas and fragrances were taken directly from forest air surrounding fragrant objects. The objective was to determine whether new products could be generated from and to investigate technology transfer options in this area. A royalty rate was established, and the agreement concluded its activities in Costa Rica in the middle of 1998.

INBio-BTG-Ecos La Pacífica

In agriculture, INBio seeks to integrate bioprospecting discoveries with the country's economic development. This process began with the 1992 INBio-British Technology Group (BTG) Agreement, which allowed INBio to begin the investigation, characterization, and manufacture of a product with nematicidal activity (DMDP) derived from a tree found in Costa Rica's dry tropical forest. At the same time, investigations were developed jointly with the corporation of Ecos La Pacífica to determine the species' growing conditions, the effectiveness of DMDP in tropical crops, and its production methods. Green-

house and field trials began in 1999; they continue to-date with very satisfactory results. BTG has paid a small amount of money to both INBio and Ecos for licensing a patent related to the use of DMDP.

INBio-Diversa: Search for enzymes from extremophilic organisms with Chemical Industry application

To explore new enzymes discovered in aquatic and terrestrial microorganisms that live under extreme conditions, INBio signed a research agreement with the DIVERSA biotechnical industry in 1995. Renewed in 1998 and 2002, the agreement gathers bacteria from different Conservation Areas of Costa Rica in order to identify and isolate novel, useful enzymes for industry. The agreement also guarantees training for Costa Rican scientists in collection methods, isolation, and molecular biology, specifically in cloning and characterizing genes associated with the enzymes.

INBio-INDENA S.P.A.: Search for compounds with antimicrobial and antiviral activity

To obtain compounds with antimicrobial potential for use as active ingredients in cosmetics, INBio and the phytopharmaceutical company INDENA (Milan, Italy) signed a collaboration agreement in 1996. Extracts from selected plants are evaluated in bioassays to determine their antimicrobial activity. The final process is carried out at INDENA. A second phase of the project began in 2000.

INBio-Phytera Inc.

Traditionally drugs have been developed from the extracts of leaves, roots, bark, and other plant parts. Advances in biotechnology now make it possible to derive them by cultivating cells, which only requires extremely small samples and can produce a diversity of chemical substances—more than when the original plant is used. In 1998 INBio signed an Agreement with Phytera Inc. to pursue this process. It concluded in 2000.

INBio- Eli Lilly: Search for new compounds

This project ran from 1999 to 2000 and searched for botanical compounds with pharmaceutical applications. As a result of this successful collaboration, Ely Lily donated to INBio technology to prepare fractions (Bioexplore), which allowed INBio to provide fraction services and improve its research and development capabilities.

INBio-Akkadix Corporation: Search for compounds with nematicidal activity

This project was carried out with the Akkadix Corporation from 1999 to 2001. Its main objective was to search for alternatives to controlling nematodes.

2.2 Agreements with Academia

INBio also has academic investigation agreements with national and international universities. These vary in focus but are all geared toward producing knowledge about our biodiversity, discovering potential novel solutions to current problems in a number of fields, and developing new products.

INBio-University of Strathclyde

This agreement provided access to new technologies and methodologies and also established connections with the Japanese private sector. INBio supplied a limited number of plant extracts for evaluation by several Japanese industries. This agreement existed from 1997 to 2000.

INBio-University of Massachusetts: Search for potential insecticides

INBio's collaboration with the University of Massachusetts to look for compounds with insecticidal activity was made possible through the support of the National Institutes of Health (NIH). This investigation began in October 1995 and concluded in 1998. It performed enzymatic bioassays on extracts of plants, insects, bryophytes, and mollusks.

INBio-University of Guelph: Development of New Technologies for Medicines based on Plants, an International Interdisciplinary initiative

This agreement with the University of Guelph was signed in 2000 and extended to 2003. The main objective was to search for new pharmaceutical products through such techniques as tissue cultivation.

2.3 Other Types of Agreements

Validation of promissory plants

This project was financed by the CR-USA Foundation. It contemplated 3 sub-projects to obtain information that could improve the quality of life in Costa Rica. In collaboration with the Center for Research and Diagnosis in Parasitologia of the University of Costa Rica (CIDPA), two plants were studied to isolate their active components against malaria. This investigation gave continuity to the excellent results of the ICBG project.

Also, in collaboration with the UME (Unit of Electronic Microscopy), LEBI (Laboratory of Biological Assays), and the National Children's Hospital, plants traditionally used to treat gastritis were validated by their anti-helicobacter pylori activity. To explore their economic feasibility, some species were also validated by alkaloid content.

The Chagas Project

INBio joined with EARTH, the National University of Costa Rica and other Latin American institutions in Brazil, Mexico, Chile, Argentina, Uruguay, and the United States (NASA) as part of "The ChagaSpace Project." This project sought a solution to one of the most serious public health problems in Latin America: Chagas disease (American Tripanosomiasis). In 1997 INBio researched plants with inhibitory activity for this disease. In 2001 the United States Congress approved a fund dedicated to financing this project again, and work on the bioassays has been restarted.

INBio-IDB: Program from Support of the Development of the Use of the Biodiversity by Small Enterprises

In February of 1999, INBio signed an agreement with the Interamerican Development Bank to formalize the terms of a grant for non-reimbursable technical cooperation to supports biodiversity development for small companies. Six projects have been approved:

1. Agrobiot S.A.: Propagation of Costa Rican tropical plants for commercialization as eco-educational souvenirs.Laboratorios Lisan S.A.: Pharmaceutical products based on medicinal plants. At least 5 natural products will be commercialized in 2004 and 2005.La Gavilana: Development of a model for eco-friendly practices in vanilla production through the identification of a biopesticide that allows for the organic production of vanilla.Industrias Caraito S.A.: Generated added value for the Carao agro-industry.Bougainvillea S.A.: Research to develop and produce a Biocide from Quassia amara wood.Follajes Ticos S.A.: Ornamental plants native to the forest and with potential for successful commercialization: Several new species are under domestication. These and other contract relationships have provided great benefits to INBio and Costa Rica, including:

- Monetary benefits through direct payments
- Payment for supplied samples
- Funds for research budgets
- The transfer of important technology enabling infrastructure development at the Institute (biotechnology lab, etc.) that can be used to investigate and generate its own products
- Training of scientists and experts in state-of-the-art technology
- Negotiation experience, particularly knowledge of the market and of the probabilities of identifying biodiversity resources for intellectual use
- Support of conservation through payments made to the Ministry of the Environment to strengthen the National System of Conservation Areas
- Transfer of equipment to other institutions, such as the University of Costa Rica.
- Future royalties and milestone payments to be shared 50:50 with the Ministry of the Environment
- Establishment of national capabilities for assessing the value of biodiversity resources.

The significance of this contract approach must not be underestimated. These contractual arrangements have made possible different joint initiatives (e.g., the Cooperative Biodiversity Groups, etc.) as well as studies on the effects of benefit sharing. Table 1 summarizes the main collaborative agreements.

Table 1: Most significant Research Collaborative Agreements with Industry and Academia (from 1991 to 2002)

Industrial or academic partner	Natural resources accessed / Objectives	Field of primary application	Research activities in Costa Rica
Cornell University	INBio's capacity building	Chemical Prospecting	1990-1992
Merck & Co	Plants, insects, micro organisms	Human health and veterinary	1991-1999
British Technology Group	DMDP, compound with nematocidal activity*	Agriculture	1992-present
ECOS	*Lonchocarpus felipei*, source of DMDP*	Agriculture	1993-present
Cornell University and NIH	Insects	Human health	1993-1999
Bristol Myers & Squibb	Insects	Human health	1994-1998
Givaudan Roure	Plants	Fragrances and essences	1995-1998
University of Massachusetts	Plants and insects	Insecticidal components	1995-1998
Diversa	DNA from Bacteria	Enzymes of industrial applications	1995-present
INDENA SPA	Plants*	Human health	1996-present
Phytera Inc.	Plants	Human health	1998-2000
Strathclyde University	Plants	Human health	1997-2000
Eli Lilly	Plants	Human health and agriculture	1999-2000
Akkadix Corporation	Bacteria	Nematocidal proteins	1999-2001
Follajes Ticos	Plants	Ornamental applications	2000-present
La Gavilana S.A.	*Trichoderma* spp*	Ecological control of pathogens of *Vanilla*	2000-present
Laboratorios Lisan S.A.	None*	Production of standardized phytopharmaceuticals	2000-present
Bouganvillea S.A.	None*	Production of standardized biopesticide	2000-present
Agrobiot S.A.	Plants*	Ornamental applications	2000-present
Guelph University	Plants*	Agriculture and Conservation purposes	2000-present
Florida Ice & Farm	None*	Technical and scientific support	2001-present
ChagasSpace Program	Plants, fungi*	Chagas disease	2001-present
SACRO	Plants*	Ornamental applications	2002-

These agreements include a significant component of technical and scientific support from INBio.

Source: Tamayo *et al* forthcoming in 2004.

2.4 Main Benefits and Research Results

The following tables list the major benefits (non-monetary and monetary) of INBio's bioprospecting agreements.

Table 2: Monetary and Non Monetary Benefits of Bioprospecting

Monetary Benefits
* 100% of research budgets
* Technology transfer and infrastructure
* Up front payments for Conservation
* Significant contribution for GCA and Universities
* Milestone and royalty payments to be shared with MINAE
Non Monetary Benefits
* Trained human resources
* Empowerment of human resources
* Negotiations expertise developed
* Market Information
* Improvement of local legislation on conservation issues

Table 3: Outputs generated since 1992 as a result of research collaboration agreements with INBio

Project	Year Initiated	Major output
Merck & Co.	1992	27 patents
BTG/ECOS	1992	DMDP on its way to commercialisation
NCI	1999	Secondary screening for anti- cancer compounds
Givaudan Roure	1995	None yet
INDENA	1996	2 compounds with significant anti-bacterial activity
Diversa	1998	2 potential products at initial stages / Publication underway
Phytera Inc.	1998	None yet
Eli Lilly & Co.	1999	None yet
Akkadix	1999	52 bacterial strains with nematocidal activity
CR-USA	1999	1 compound with significant anti-malarial activity
LISAN	2000	2 phytopharmaceuticals in the process
Caraito	2000	None yet
Follajes ticos	2000	None yet
Bougainvillea	2001	None yet
La Gavilana	2001	None yet
Agrobiot	2001	None yet
SACRO	2002	None yet

Source: Tamayo *et al*. Forthcoming in 2004.

Table 4: Contribution to Biodiversity Conservation in Costa Rica
(US$ x 1,000)

	1993*	1994	1995	1996	1997	1998	1999	2000	Total
Ministry of Environment and Energy	110	43	67	51	95	24	39	87	516
Conservation Areas (Development of Bio-prospecting Research)	86	203	154	192	126	30	0	0	791
Costa Rican Public Universities	460	126	47	31	35	14	7	4	724
Other groups in INBio	228	93	118	173	129	0	0	0	741
Total	**884**	**465**	**386**	**447**	**385**	**68**	**46**	**91**	**2,772**

1) Estimated amounts since 1991.

2.5 Legal Considerations

In Costa Rica, genetic and biochemical resources are the property of the State, with qualifications regarding public goods. In the case of indigenous territories and the public or private ownership of the lands or biological resources containing the genetic and biochemical resources, the owners' prior informed consent is required for access. But this does not grant them a right of property for the genetic and biochemical components. The law requires the applicant to attach the prior informed consent for access granted by the owner of the land, by the authority of the indigenous community, or by the Director of the Area of Conservation (Article 65, Law of Biodiversity).

Costa Rica's Law of Biodiversity No. 7788 of 27 May 1998 applies to biodiversity components that are under the State's sovereignty and to the processes and activities carried out under its jurisdiction or control, independently from those effects manifested inside or outside of the national jurisdiction. This Law specifically regulates the use, management, associated knowledge, and sharing of the benefits and derived costs of utilizing biodiversity components (Article 3). Also, Article 6 (public domain) establishes that the biochemical and genetic properties of the components of wild or domesticated biodiversity belong to the public domain. The State authorizes the exploration, research, bioprospecting, use, and utilization of biodiversity components that are public domain, as well as the use of all genetic and biochemical resources, through access standards established in Chapter V of this Law. Likewise, in accordance with Articles 62 and 69, all research or bioprospecting programs on genetic or biochemical biodiversity material to be carried out in Costa Rican territory require an access permit, unless for exceptions provided under this Law. These exceptions (Art 4) basically refer to access to human genetic resources, the exchange of genetic and biochemical resources, and the traditional associated knowledge resulting from the traditional practices of indigenous peoples and local communities when they are non-profit. Public Universities have one year (up to May 7 1999[5]) to establish their own controls and regulations for their research that imply access and are non-profit. If it is not so, all the sectors (pharmaceuticals, agricultural, crop protection, biotechnology, ornamental, herbal, etc.) accessing genetic components are subject to the Law's application and should follow the access procedures.

[5] Only the University of Costa Rica developed its own Regulation of Access regimes.

In this regard, the access regulations are applied to genetic resources in public or private lands, terrestrial or marine environments, under *ex situ* or *in situ* conditions, and in indigenous territories.[6] Likewise, relevant access provisions of the Law are applied to indigenous territories, but additionally their own rules should be taken into account, as well as *sui generis* community intellectual rights. Similarly, communities and indigenous peoples have the right to oppose access to their resources and associated knowledge for cultural, spiritual, economic, or other reasons.

2.6 Difficulties and Challenges for Implementing Legal Frameworks: The case of Costa Rica[7]

In 1998 Costa Rica enacted its Biodiversity Law. It regulates access to genetic and biochemical resources and the sharing of benefits resulting from their use. The following sections summarize the main difficulties and challenges that Costa Rica has faced in developing its Biodiversity Law.

Uncertainty and value

- Bioprospecting is very uncertain; the word "bioprospecting" was derived from prospecting for oil and minerals, but prospecting for biological and genetic resources—or even for indigenous knowledge—is quite different. The risks are greater. Although many samples have been collected from all over the world since the mid-1980s, only a few products have reached the clinical or even pre-clinical stage.
- When determining the value of genetic resources it must be remembered that the significance of one sample in the overall chain of efforts and costs required to develop a new product or a new drug is very limited. If a country can add value to these resources (e.g., by scientific research), then their value and benefits can increase.
- Technology has had a paradoxical impact on the value of biological resources. On the one hand, new technologies increase the potential for the commercial use—and thereby the economic value—of biological resources because the cost of screening these materials and/or isolating active ingredients is decreasing. On the other hand, technological developments have reduced the amount of material needed for research purposes, and this may facilitate illegal collection and use. In general, the economic value of genetic resources is increasing, but the commercial value of any particular extract or sample is not.

Rights and ownership

In regards to property rights and ownership, the CBD does not address the question of ownership; it only establishes (Article 3) that states are sovereign over their genetic and biological resources. But sovereignty, national patrimony, and ownership are different concepts; therefore, it is important to clearly define ownership in the national law. In fact, some of the most common problems that arise when negotiating benefit sharing agreements are related to a lack of clarity about ownership. In Costa Rica, the Law divides biodiversity property rights into genetic and bio-chemical properties and the biological resources *per se*. Biochemical and genetic properties belong to the State and are therefore under the administration of the Ministry of the Environment and Energy, while biological resources are the

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[6] Article 2 (Area of application) of the Draft Regulations on Access states that it shall be applied on genetic and biochemical elements of wild or domesticated biodiversity, *in situ* or *ex situ*, under State Sovereignty, that are public or private propriety.

[7] This section principally draws Sittenfeld, Cabrera and Mora (2003).

property of the landowner, a situation that causes confusion and stirs debates about definitions and use intentions.

Over-regulation

Another notorious pitfall is over-regulation:

- The complexity of access regulations creates problems; if nobody can comply with the regulations, then they will likely not be enforced. High transaction costs and bureaucratic procedures also contribute to poor enforcement.
- Access legislation may negatively affect basic research; it may have negative impacts on local universities and research institutions because basic research is important for conservation purposes and for sustaining biodiversity.

Defeating the purpose?

The ultimate goal of access and benefit sharing should be clear. If the main aim is to make money, it is bound to fail. If the objective is to create national capacity, a value added industry, or the conservation of natural biological resources, then it is necessary to make the right connections and develop coherent policies on access, biodiversity conservation, and sustainable use. These policies should include access to knowledge and the traditional use of medical products. Considerations about different treatments or regulations according to the initial nature or purpose of research (non-commercial versus research intended for commercial development) have led to discussions about whether or not to consider all intended research that has the potential to send products into the market place sooner or later.

3. Lessons Learned

A. There must be a clear institutional policy for the criteria demanded in prospecting contract negotiations. For INBio, these include the transfer of technology, royalties, limited quantity and time access, limited exclusiveness, no negative impacts on biodiversity, and direct payment for conservation. This policy has led to the stipulation of minimum requirements for initiating negotiations, and these requirements have meant rejecting some requests (e.g., very low royalties, unwillingness to grant training, etc.). This institutional policy also provides greater transparency and certainty for future negotiations. These same policies must also be taken into consideration when local communities and indigenous peoples, such as the Kuna's in Panama, adopt legal outlines (Cabrera, 1997) in the contractual arrangements entered into by them. They should include other relevant ideas, such as those related to the impossibility of patenting certain elements, licensing instead of a complete transfer, etc.

B. The existence of national scientific capabilities, and consequently, the possibilities of adding value to biodiversity elements, increases the negotiating strengths and benefit sharing stipulated in contract agreements. As we previously mentioned, the need to grant an aggregated value to material, extracts, etc., is crucial if one wishes to be more that just a simple genetic resource provider. In this regard, the development of important human, technical, and infrastructure capacities through laboratories, equipment, etc., together with the institution's prestige, have permitted better negotiation conditions.

The existence of relevant traditional knowledge for operations, which INBio has not yet experienced, implies greater scientific capacity and, consequently, should lead to better compensation conditions.

C. Knowledge of operational norms and of the changes and transformations taking place in the business sector, as well as the scientific and technological innovations that underlie these transforma-

tions, helps to define access and benefit sharing mechanisms. It is essential to know how different markets operate and what access and benefit sharing practices already exist in these markets. These vary from sector to sector: the market dynamics for nutraceuticals, ornamental plants, crop protection, cosmetics, and pharmaceuticals are complex and different (see for example Ten Kate and Laird 1999). This knowledge is needed to correctly negotiate royalties and other payment terms. How can we otherwise know if a percentage is low or high? It is also crucial to be informed about the operational aspects of these markets. When INBio began negotiating new compensation forms, such as advance payments or payments on reaching predefined milestones, with Eli Lilly and Akkaddix, it was vitally important to know the approximate amounts the industry was likely to pay in order to negotiate appropriately. Otherwise, one will likely request terms that are completely off the market or accept terms that are inadequate.

D. Internal capacity for negotiations, which includes adequate legal and counseling skills about the main aspects of commercial and environmental law. The Institute now recognizes that negotiations involve a scientific aspect (of crucial importance to define key areas of interest such as a product, etc.), a commercial aspect, a negotiation aspect, and the respective legal aspects. These latter are comprised not only of national trade law but also international environment law, conflict resolution, and intellectual property. For these reasons, creating interdisciplinary teams is crucial (Sittenfeld and Lovejoy, 1998). At the same time, the need for such a team is one of the most important criticisms of the contractual mechanisms. Solutions such as facilitators or others that pretend to "level the negotiation power" have been proposed by several authors. Unfortunately, until appropriate multilateral mechanisms exist, benefit sharing and contractual systems must go hand in hand. The absence of an interdisciplinary team keeps one of the parties at a disadvantage, particularly given the enormous legal and negotiation capabilities of pharmaceutical companies.

E. Innovative and creative ideas for obtaining compensation. An ample spectrum of potential benefits exists. In the past, interesting benefit sharing formulas were developed through appropriate negotiations. Such formulas included, for example, fees for visiting gene banks, collecting material, etc. The contractual path fortunately permits parties to adapt themselves to the unique situation of each concrete case and to proceed from there to stipulate new clauses and dispositions.

F. Understanding in such key subjects as: intellectual property rights; the importance of warranties for legality; clauses on ways to estimate benefits (net, gross, etc.); requirements and restrictions on third party transference of material (including subsidiaries, etc.) and the obligations of such parties; precise definitions of key terms that condition and outline other important obligations (products, extracts, material, chemical entity, etc.); precise determination of property and ownership (IPR and others) of the research results, joint relationships, etc.; confidentiality clauses in the agreements and how to balance them in relation to the need for transparency in the agreement; termination of obligations and the definition of the survivor of some obligations and rights (e.g., royalty, confidentiality, etc.); conflict resolutions.

As sub-clause D makes very clear, negotiated agreements are complex. For example, the outcomes that give rise to benefit sharing, such as royalties, will depend on the nature of the definitions for "product", "extract", "entity", etc. A more comprehensive definition will lead to a better position. Further examples of aspects that must be specified include delimiting the areas or sectors where samples can be used, the net sales, and what is possible to exclude from them. In addition, the procedures and rights in the case of joint and individual inventions are of interest (preference and acquisition rights, etc.), as are the conditions for the transfer of material to third parties (under the same terms as the main agreement? need for consent or information? transference to third parties so that certain services can be performed? etc.).

G. Proactive focus according to institutional policies. There is no need to remain inactive while waiting for companies to knock on the door to negotiate. An active approach to negotiations based on

the institution's own policy for understanding national and local requirements has produced important benefits. INBio's Business Development Office and its highly qualified expert staff, the attendance of seminars and activities with industry, the distribution or sharing of information and material, and direct contacts, all of these empower an institution to deal with challenges. The current policy is based on the idea that it is not enough to wait to be contacted or to be available at the behest of a company; instead, one should possess and maintain one's own approach.

H. Understanding national and local needs in terms of technology, training, and joint research. International strategic alliances must be struck. Even when an institution or community possesses adequate resources to face a concrete demand, knowing the national situation and the strategic needs will permit it to reach better agreements and fulfill a mission that goes beyond merely satisfying the institution's interests. It will permit the prospecting to benefit society as a whole and demonstrate that it is possible to improve quality of life.

I. Macro policies and legal, institutional and political support. For prospecting to succeed, so-called macro policies have to exist (Sittenfeld and Lovejoy, 1998); that is to say, there must be clear rules about the "bioprospecting framework," which requires biodiversity inventories, information systems, business development, and technology access. One reason for Costa Rica's success is that institutions not only have experience in negotiation but also in setting policies and actions in this area overall. This includes, for example, a current biodiversity inventory rated as "successful" that enables us to know what we possess. It is the first step in the quest to use this resource intelligently. Our relevant experience also includes a National Conservation Area System that assures the availability of resources, the possibility of future supplies and provisions, mechanisms that contribute to the conservation of biodiversity as part of the contractual systems, etc. At the same time, the possibility of possessing adequate instruments to manage information, systems of land and property ownership, etc., contribute jointly with the existing scientific capacity to create a favorable environment for bioprospecting and to make possible the negotiation and attraction of joint enterprises. To this should be added other elements, such as the existence of trustworthy partners, which is one of the most relevant aspects in joint undertakings (see Sittenfeld and Lovejoy, 1998).

Lastly, one crucial topic is the constant denouncement of the business community because of the uncertainty caused by the new access rules (mainly in terms of who is the competent authority, the steps to be taken, how to secure prior informed consent, etc.) The emergence of these new regimes, together with the fact that the intention is to essentially control genetic information, its flow, supply, and reception—a topic where little national, regional, and international experience exists—has caused concern because of the possibility of contravening legal provisions. This has led to the establishment, as a policy, of the inclusion of clauses related to the need to fulfill local regulations, to demonstrate the contracting parties' right to fulfill their obligations pursuant to national laws, to present the appropriate permits and licenses, etc. In some cases, this topic has generated important discussions and analyses in negotiations. At an international level, various bio-prospecting agreements around the world are the target of complaints, claims, and lawsuits precisely due to the lack of legal certainty. This has created problems and discrepancies that hinder activities and joint ventures. A few examples would be complaints about the Agreement between Diversa and the Autonomous University of Mexico (which is still being litigated); or the deal between this company and Yellowstone National Park; or criticisms of the agreement between the Venezuelan Ministry of the Environment and the Federal University of Zurich.

4. Conclusions

The case of Costa Rica has interesting individual features that make it worthy of consideration, but it is not necessarily an example to be followed by other nations. The peculiar circumstances of its national reality (see Mateo 1996 and 2000 for these special situations), the size of the country, the structure of

the central government, its political, educational, and social situation, among others, have led to the establishment of important but unique conditions. It is, however, an example of a nation that chose a path instead of continuing to discuss the difficulties of potentially traveling on one. From this perspective, the practical experiences of access and benefit sharing embodied in contracts and collaboration treaties with the public and private sectors at the national and international levels, the creation of a Law of Biodiversity that seeks to answer the challenges made by the Convention, the regulation of general *sui generis* systems principles, etc., are all concrete elements that to ground further debate, and this is probably the most valuable aspect of our experience.

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